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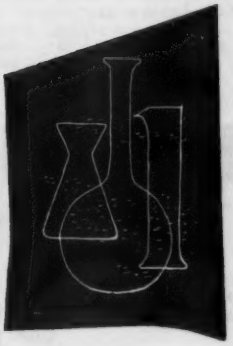
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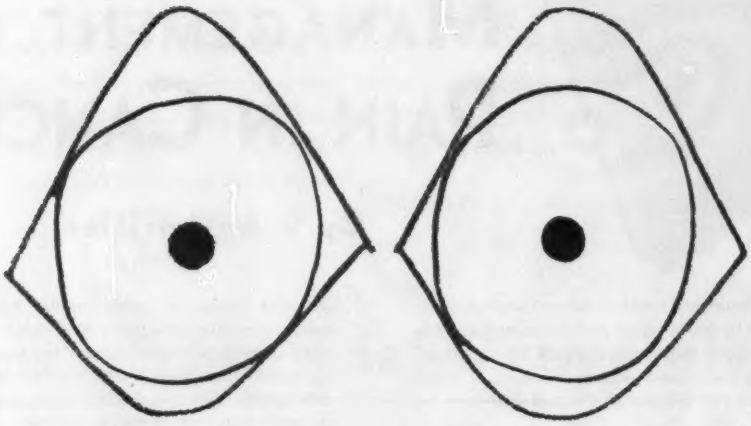
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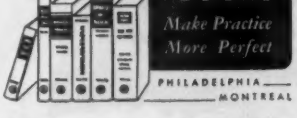
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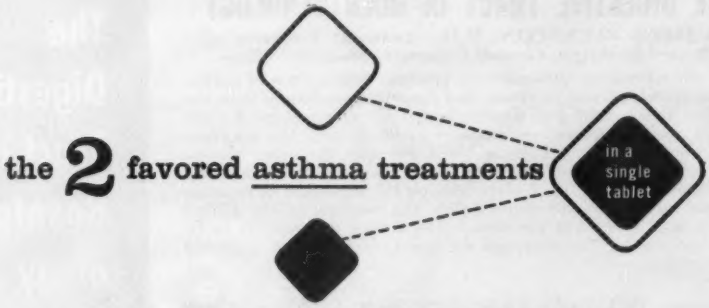
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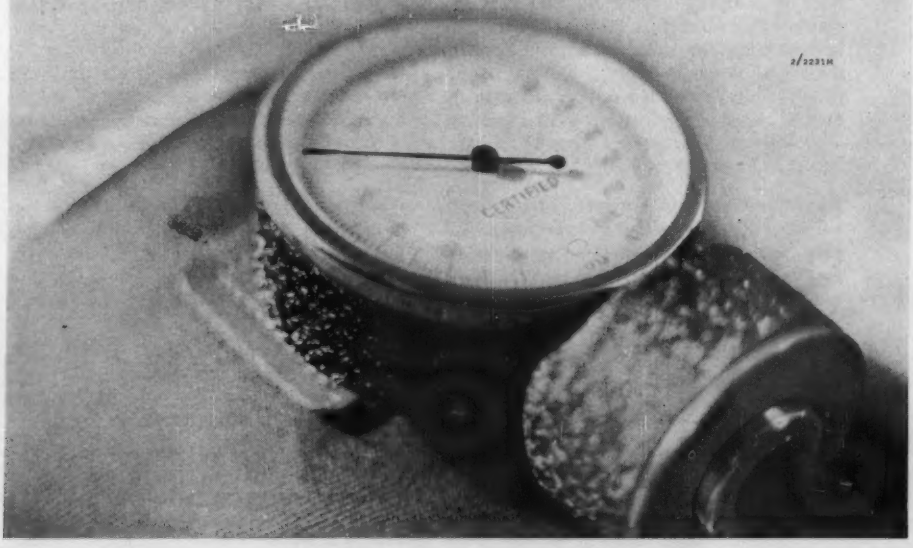
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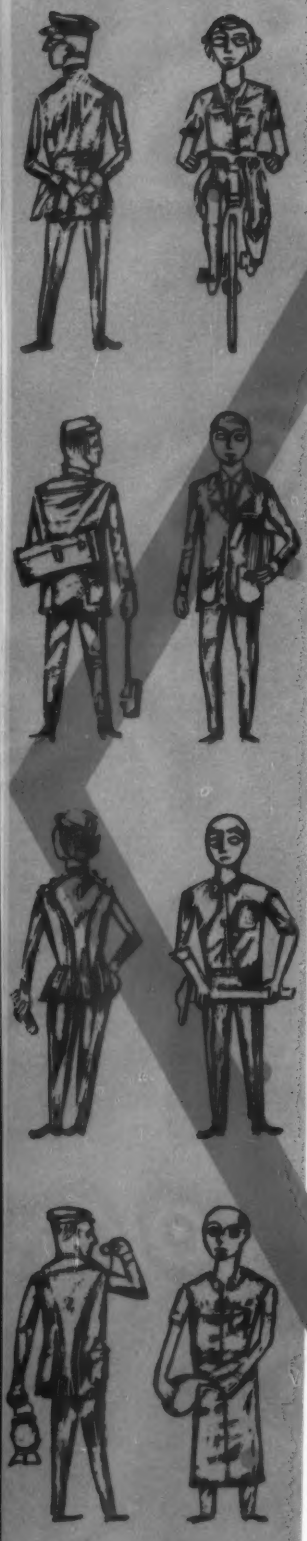
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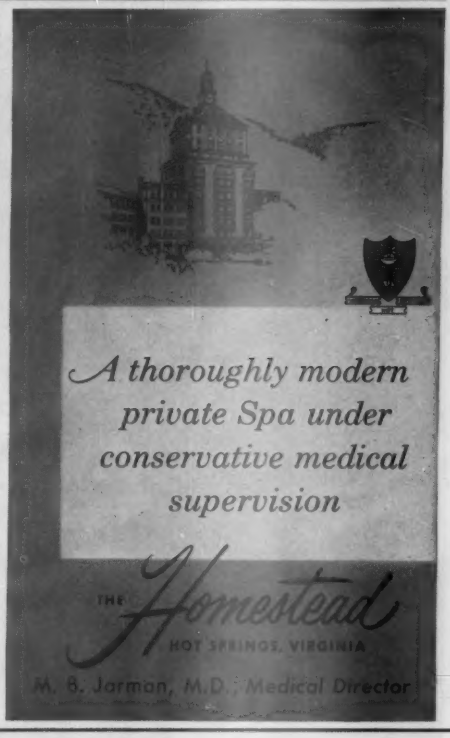
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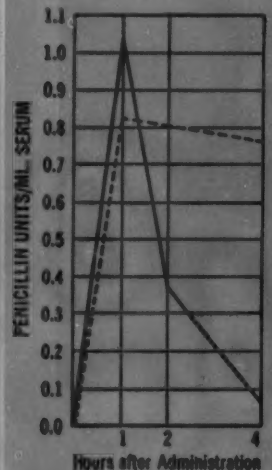
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This ready-mixed, stable, and pleasantly flavored suspension is supplied as follows: PEN·VEE·*Suspension*, 300,000 units per 5-cc. teaspoonful, bottles of 2 fl. oz. Also available: PEN·VEE·*Oral* Tablets, 200,000 units, scored, bottles of 36; 500,000 units, scored, bottles of 12.

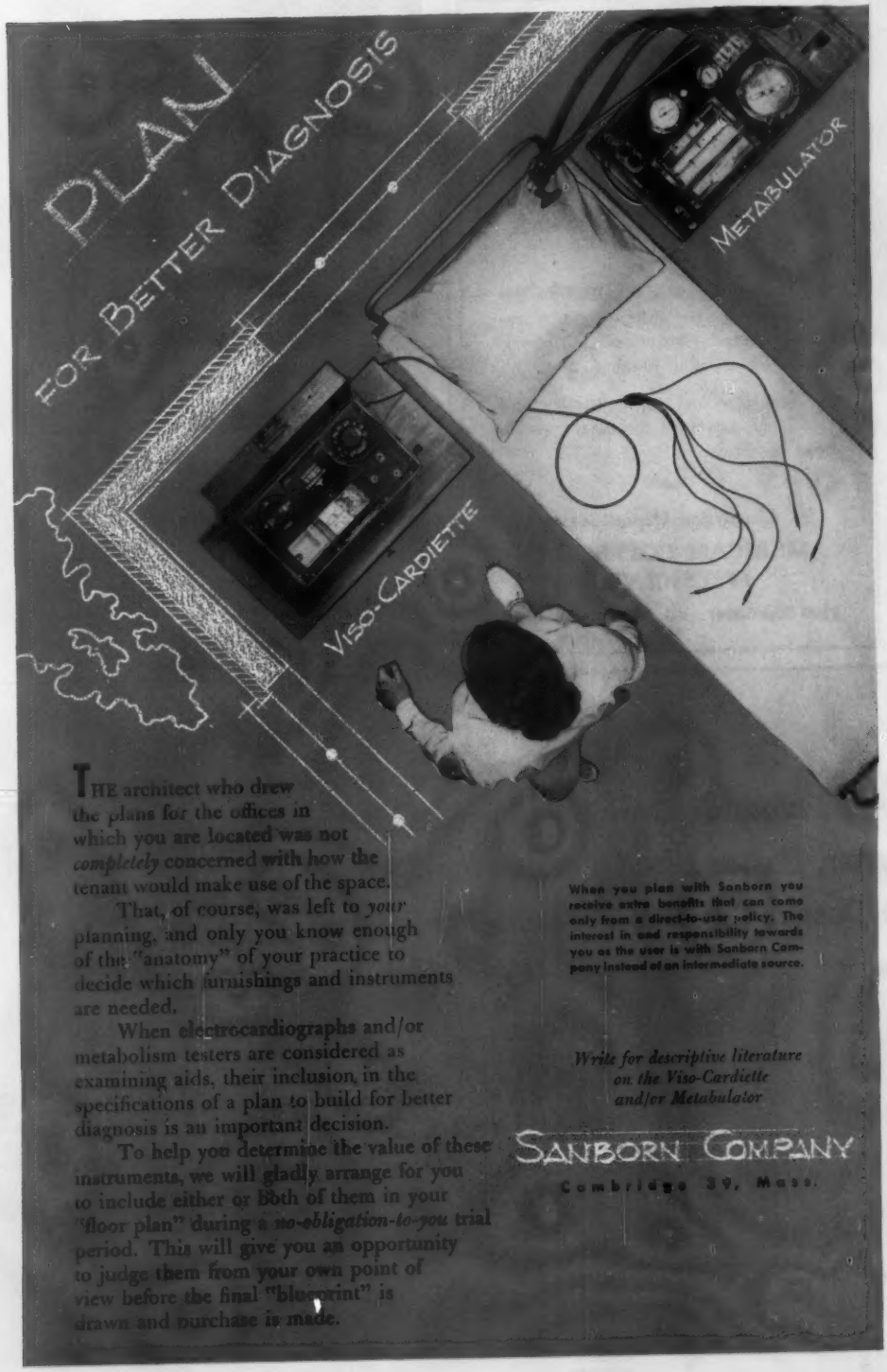
PEN·VEE*·*Suspension*

Benzathine Penicillin V Oral Suspension

ORAL PENICILLIN WITH *INJECTION* PERFORMANCE

Wyeth Philadelphia 1, Pa.

*Trademark



THE architect who drew the plans for the offices in which you are located was not *completely* concerned with how the tenant would make use of the space.

That, of course, was left to *your* planning, and only you know enough of the "anatomy" of your practice to decide which furnishings and instruments are needed.

When electrocardiographs and/or metabolism testers are considered as examining aids, their inclusion in the specifications of a plan to build for better diagnosis is an important decision.

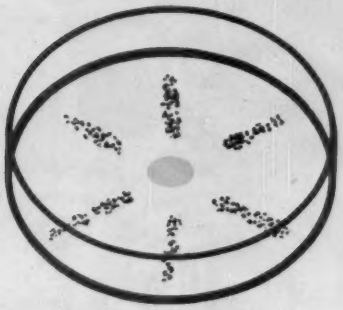
To help you determine the value of these instruments, we will gladly arrange for you to include either or both of them in your "floor plan" during a *no-obligation-to-you* trial period. This will give you an opportunity to judge them from your own point of view before the final "blueprint" is drawn and purchase is made.

When you plan with Sanborn you receive extra benefits that can come only from a direct-to-user policy. The interest in and responsibility towards you as the user is with Sanborn Company instead of an intermediate source.

Write for descriptive literature on the Viso-Cardiette and/or Metabulator

SANBORN COMPANY
Cambridge 39, Mass.

IN URINARY TRACT INFECTIONS



sensitivity studies suggest

FURADANTIN's "broad spectrum of antibacterial and antiprotozoal activity *in vitro*"[1] makes it important to include this agent, routinely, in sensitivity tests. Organisms commonly resistant to most of the antibiotics, notably Proteus and Pseudomonas, are often inhibited by FURADANTIN.[2]

Furadantin®

BRAND OF NITROFURANTOIN

". . . may be unique as a wide-spectrum antimicrobial agent that is bactericidal, relatively nontoxic, and does not invoke resistant mutants."[3]



clinical cures confirm

"Clinical studies have demonstrated rapid clinical response of cases of cystitis, prostatitis, and pyelonephritis."[4]

Typical Timetable of Furadantin Effectiveness

In *30 minutes,* antibacterial concentrations in urine.

In *24 hours,* turbid urine is usually clear.

In *3 to 5 days,* most patients are symptom-free and the urine is free of pus cells.

In *one week,* the urine is usually sterile.

SUPPLIED: Tablets, 50 and 100 mg., bottles of 25 and 100.
Oral Suspension, 5 mg. per cc., bottle of 118 cc.

REFERENCES: 1. Mintzer, S., et al.: Antibiotics 3:151, 1953. 2. Felton, F. C., and Kemp, A. P.: J. Urol. 73:718, 1955. 3. Waisbren, B. A., and Crowley, W.: A.M.A. Arch. Int. M. 98:653, 1956. 4. Flippin, H. F., and Eisenberg, G. M.: Antimicrobial Therapy in Medical Practice, Philadelphia, F. A. Davis Company, 1955, p. 40.

EATON LABORATORIES, Norwich, N.Y. NITROFURANS a new class of antimicrobials neither antibiotics nor sulfas

in arthritis
and
allied disorders...



nonhormonal anti-arthritic

BUTAZOLIDIN®

(brand of phenylbutazone)

relieves pain • improves function • resolves inflammation

Employing the serum protein-polysaccharide ratio (PR) as an objective criterion of rheumatoid activity, it has again been shown that BUTAZOLIDIN "...produces more than a simple analgesic effect in rheumatoid arthritis."[1]

Clinically, the potency of BUTAZOLIDIN is reflected in the finding that 57.6 per cent of patients with rheumatoid arthritis respond to the extent of "remission" or "major improvement."[2]

Long-term study has now shown that the failure rate with BUTAZOLIDIN in rheumatoid arthritis, and particularly in rheumatoid spondylitis, is significantly lower than with hormonal therapy.[3]

(1) Payne, R. W.; Shetlar, M. R.; Farr, C. H.; Hellbaum, A. A., and Ishmael, W. K.: J. Lab. & Clin. Med. 45:331, 1955. (2) Bunim, J. J.; Williams, R. R., and Black, R. L.: J. Chron. Dis. 1:168, 1955. (3) Holbrook, W. P.: M. Clin. North America 39:405, 1955.

BUTAZOLIDIN® (brand of phenylbutazone). Red coated tablets of 100 mg.

BUTAZOLIDIN being a potent therapeutic agent, physicians unfamiliar with its use are urged to send for literature before instituting therapy.

GEIGY PHARMACEUTICALS Division of Geigy Chemical Corporation
220 Church Street, New York 13, N. Y.
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intramuscular
intravenous

most convenient
digitalis
preparation...
change route
any time
without changing
dose or interval

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Now with Digitaline Nativelle Intramuscular, a complete range of routes of administration is available. This preparation—specifically designed for I.M. use—avoids irritation often encountered when I.V. forms are administered intramuscularly. The dosage schedule with DIGITALINE NATIVELLE need never be changed because of change in the route of administration. The same advantages are provided by all forms, enabling the physician to cope with any change in the patient's status. Prescribe DIGITALINE NATIVELLE—the original pure crystalline digitoxin • pure active principle • complete absorption • rapid onset of action • smooth, even maintenance • frequent dosage readjustment unnecessary • virtual freedom from gastric upset

Consult your Physicians' Desk Reference for dosage information.

VARICK Pharmacal Company, Inc.
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New, Well Tolerated Medium for Excretory Urography

94%

DIAGNOSTIC FILMS

in a series of 1123 patients

Hypaque SODIUM
50% solution

Write for detailed literature or consult your local Winthrop representative.

Winthrop LABORATORIES
NEW YORK 18, N.Y. • WINDSOR, ONT.

Hypaque sodium, brand of diatrizoate sodium (sodium 3,5-diacetamido-2,4,6-triiodobenzoate)

put busy patients and peptic ulcers at ease

PRANTAL Repetabs

***during the day*—8 hours' pain relief following a single dose**

***nightlong protection*—full night's sleep following bedtime dose**

PRANTAL REPETABS, 100 mg.

other dosage forms for every phase of therapy

PRANTAL Tablets, 100 mg.—*to initiate therapy, adjust dosage*

PRANTAL Injection, 25 mg. per cc., 10 cc. vials or 1 cc. ampuls —*rapid relief in emergencies, acute episodes*

PRANTAL 100 mg. with Phenobarbital 16 mg. Tablets—*when sedation is desired*

PRANTAL® methylsulfate, brand of diphemanil methylsulfate.
REPETABS,® Repeat Action Tablets.

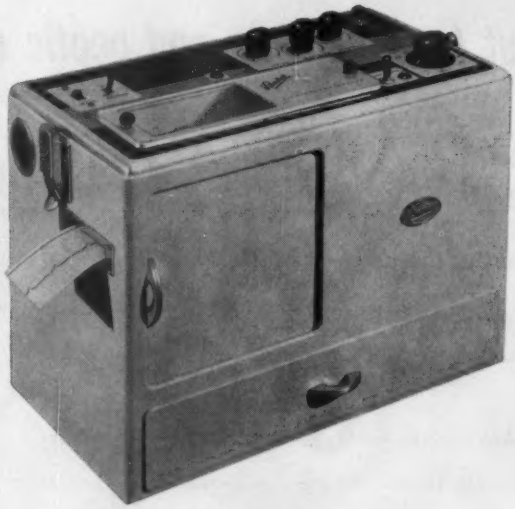
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SIMPLICITY
+
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Burdick engineers designed the EK-2 Electrocardiograph to meet the exacting standards of the medical perfectionist.

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A descriptive brochure and the name of the nearest Burdick dealer will be sent on request.

THE BURDICK CORPORATION Burdick MILTON, WISCONSIN

Cremomycin.

SULFASUXIDINE® – NEOMYCIN SUSPENSION WITH PECTIN AND KAOLIN

new – for prompt diarrhea control, quick return to work

MAJOR ADVANTAGES: Combines 'Sulfasuxidine' with neomycin for broader antibacterial action. Pectin and kaolin have soothing, detoxifying properties. Fruit flavor tastes good.



In diarrhea—whether specific or nonspecific—prompt relief is assured with CREMOMYCIN. 'Sulfasuxidine' and neomycin have a wide range of effectiveness—their combined action is complete and prompt, and they are virtually nontoxic.

In addition to the antibacterial components, kaolin and pectin in CREMOMYCIN provide adsorbent and detoxicant action, soothe inflamed intestinal mucosa. The fine subdivision of all ingredients in CREMOMYCIN increases its efficacy.

Each fl. oz. (30 cc.) of CREMOMYCIN contains 3.0 *Gm.* 'Sulfasuxidine,' 300 *mg.* neomycin sulfate, 0.3 *Gm.* pectin and 3.0 *Gm.* kaolin. Supplied in 8 oz. bottles.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.



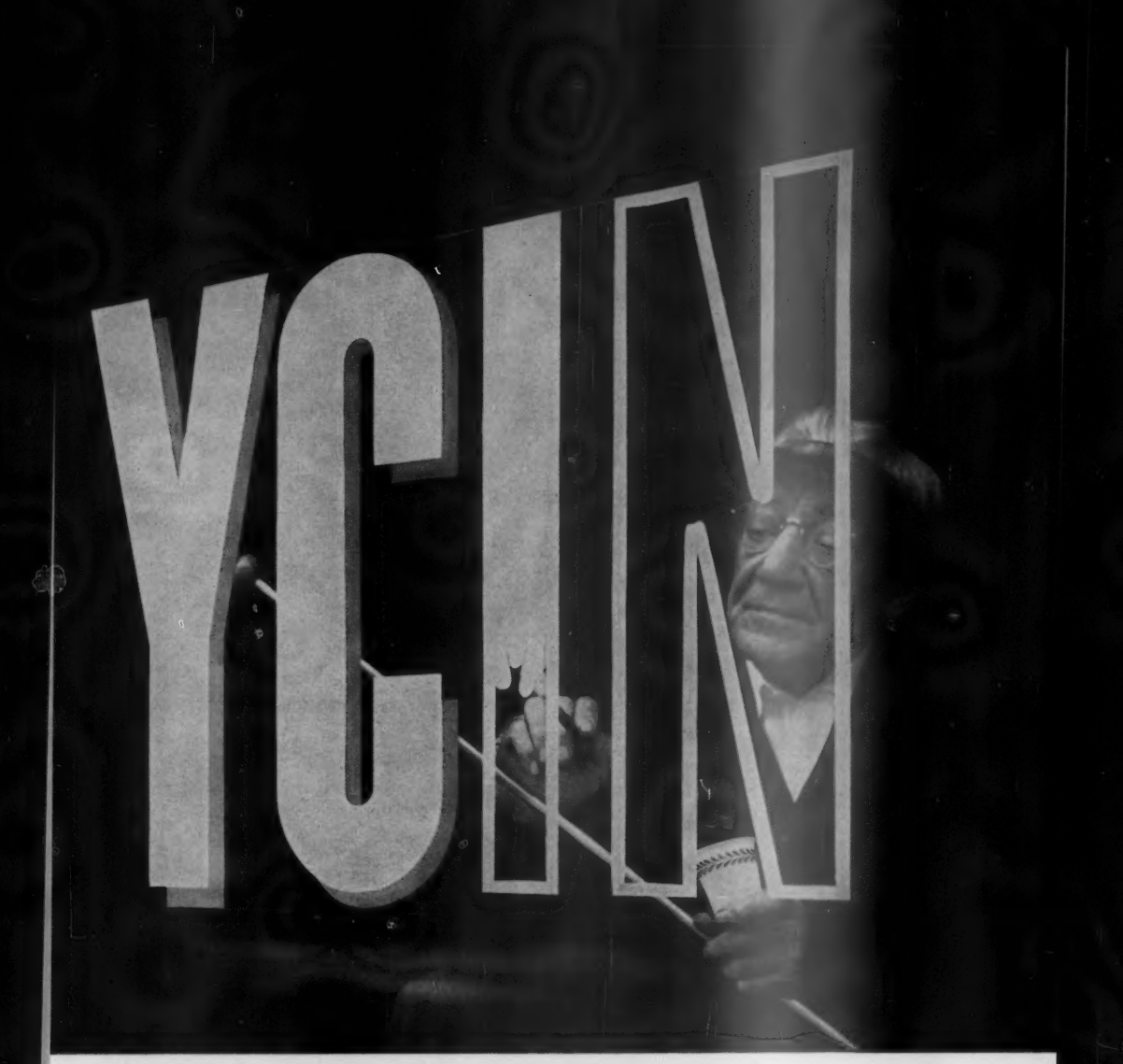
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Tetracycline
Lederle

widely prescribed because of these important advantages:

1) rapid diffusion and penetration
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3) true broad-spectrum activity (proved effective against a wide variety of infections caused by Gram-positive and Gram-negative bacteria, rickettsiae, and certain viruses and protozoa)
4) negligible side effects
5) every gram produced in Lederle's *own* laboratories under rigid quality control, and offered *only* under the Lederle label
6) a *complete* line of dosage forms



in prolonged illness, prescribe

ACHROMYCIN SF

TETRACYCLINE with STRESS FORMULA VITAMINS

Attacks the infection, bolsters the body's natural defense. Stress vitamin formula suggested by the National Research Council in *dry-filled, sealed* capsules with ACHROMYCIN, 250 mg. Also available: ACHROMYCIN SF ORAL SUSPENSION (Cherry Flavor), 125 mg. per 5 cc. plus vitamins.



filled sealed capsules
(a Lederle exclusive!) for more rapid and complete absorption. No oils, no paste, tamperproof!

LEDERLE LABORATORIES DIVISION *American Cyanamid Company* PEARL RIVER, NEW YORK Lederle

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NOW

Ferrous Iron with Vitamin C

for simple
specific
rapid
economical

correction of iron deficiency anemias

"Optimal absorption of iron is best assured by administering it in the ferrous form with ascorbic acid . . ."*

"CYTOFERIN" —*the logical combination for iron therapy.*

- Iron in the readily absorbed ferrous form.
- Vitamin C to maintain acidity in the upper intestinal tract for greater iron absorption.
- Vitamin C as a reducing agent for the ferric iron obtained from food.
- Vitamin C for hypochromic microcytic anemias, which will not respond to oral iron therapy alone.

"CYTOFERIN" —*the direct approach to greater iron absorption.*

Each tablet contains:
Ferrous sulfate exsic. (3 gr.) . . . . . 200 mg.
Vitamin C (ascorbic acid) . . . . . 150 mg.

NEW PRODUCT

Dosage: 1 tablet two or three times daily, taken preferably with meals.

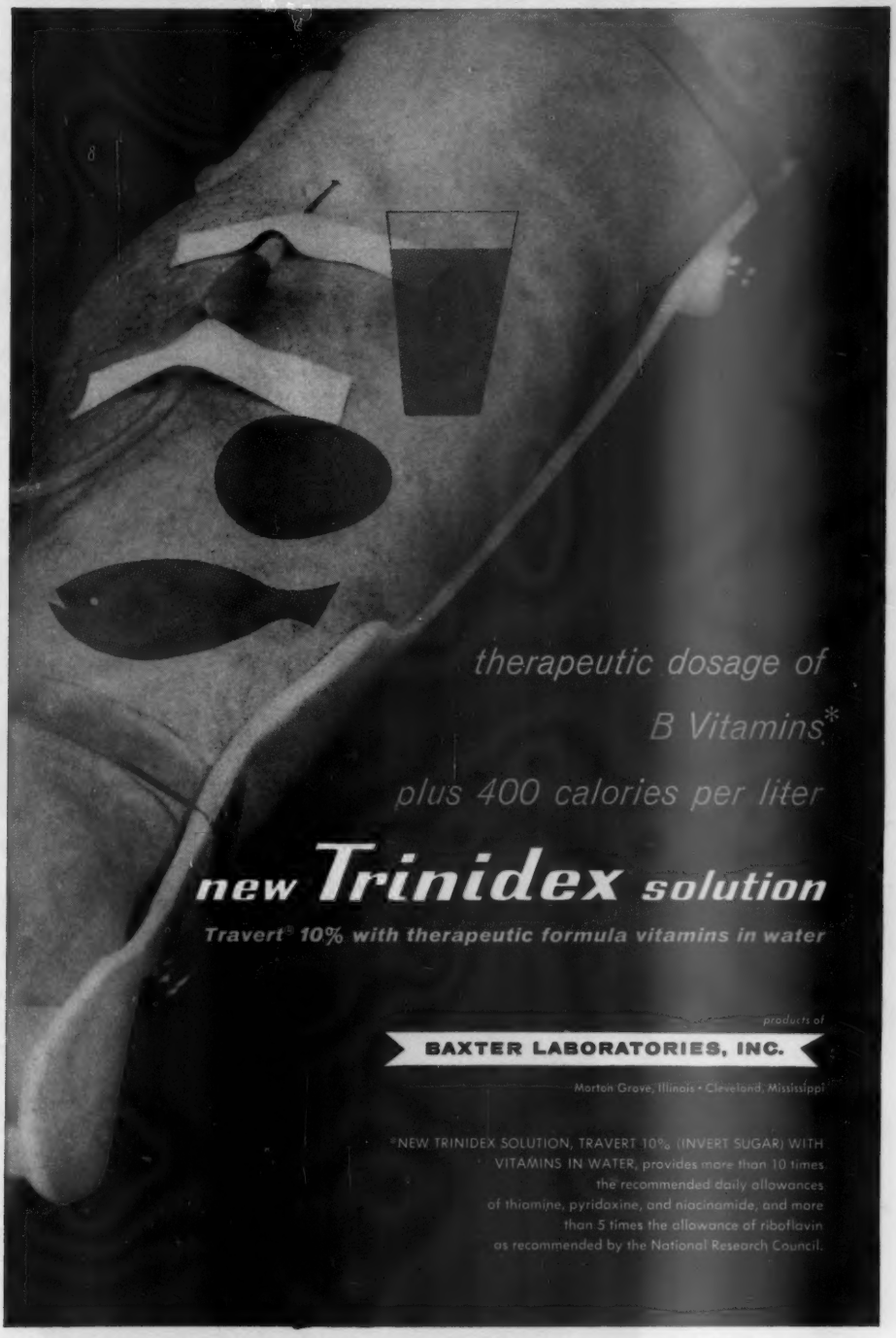
Supplied: No. 705, bottles of 100 and 1,000.

*Sacks, M. S.: Ann. Int. Med. 42:458 (Feb.) 1955.

Ayerst

Ayerst Laboratories • New York, N. Y. • Montreal, Canada

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Pharmaceuticals

NEW
normal physiological approach
to OSTEOARTHRITIS

neuritis • sciatica • neuralgia •
gout • rheumatoid arthritis

QUICK
relief from pain

high-level analgesia of DIPYRONE . . . plus antirheumatic Salrin (salicylamide, W-T) . . . aids the patient to return to more normal, comfortable living.

ATTACK
on degenerative process

glucuronic acid encourages repair of connective and fibrous tissue.

GLU-SALGIN Capsules Warren-Teed:
glucuronolactone 2½ grs.,
Salrin (salicylamide, W-T) 5 grs.,
dipyrona 1½ grs.
Bottles of 100 and 500.

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GLU-SALGIN
CAPSULES

THE WARREN-TEED
PRODUCTS COMPANY
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One-tube economy **plus** two-tube performance



YOURS with the 200-ma MAXICON® X-ray Unit



This modestly priced single-tube unit brings you fully professional radiographic and fluoroscopic facilities. These include the generous full-length table . . . broad-coverage independent tube stand . . . powerful 200-ma transformer . . . high-power rotating-anode tube. You also get:

Full-wave rectification — Brings you *full* 200-ma power for clear, sharp radiographs. Shorter exposures stop motion even when working with obese patients.

Quality that cuts costs — Professionally scaled components mean economical, dependable service.

Room to grow — Later, should you desire to expand your Maxicon installation, you can add a separate under-table tube.

No need to buy! — If you prefer, enjoy all these advantages on the G-E Maxiservice® rental plan with *no* capital investment. Your G-E x-ray representative will give you full details . . . or write X-Ray Department, General Electric Company, Milwaukee 1, Wis., for Pub. M31.

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more than
42,000,000
doses of ACTH
have been given

HP*ACTHAR® *Gel*

The Armour Laboratories brand of purified adrenocorticotropic hormone—corticotropin (ACTH)

Unsurpassed in safety and efficacy

In a series of patients treated continuously with Armour ACTH for at least 5½ years[1] . . .

- Each responded with a maintained increase in cortical function
- Major and minor surgical and obstetrical procedures caused no incidents
- Sudden discontinuance of ACTH did not provoke a crisis



. . . and HP*ACTHAR *Gel* should be used routinely to minimize adrenal suppression and atrophy in patients treated with prednisone, prednisolone, hydrocortisone and cortisone.

HP*ACTHAR *Gel* is the most widely used ACTH preparation

*Highly purified

1. Wolfson, W. Q.: Mississippi Valley M. J. 77: 66, 1955.

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A DIVISION OF ARMOUR AND COMPANY • KANKAKEE, ILLINOIS

fresh mixed

FOLBESYN*
VITAMINS LEDERLE
B+C
COMPLEX

assures full potency

Separate packaging of dry vitamins and diluent (mixed immediately before injection) assures the patient a more effective dose. May also be added to standard IV solutions.

Dosage: 2 cc. daily.

Each 2 cc. dose contains:

Thiamine HCl (B_1)	10 mg.
Riboflavin (B_2)	10 mg.
Niacinamide	50 mg.
Pyridoxine HCl (B_6)	5 mg.
Sodium Pantothenate	10 mg.
Ascorbic Acid (C)	300 mg.
Vitamin B_{12}	15 mcgm.
Folic Acid	3 mg.

Lederle

LEDERLE LABORATORIES DIVISION
AMERICAN Cyanamid COMPANY
PEARL RIVER, NEW YORK

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Gentle
is the word
for Noludar—

Mild, yet positive in action, Noludar 'Roche' is especially suited for the tense patient who needs to relax and remain clear-headed - or for the insomniac who wants a refreshing night's sleep without hangover. Not a barbiturate, not habit-forming. Tablets, 50 and 200 mg; elixir, 50 mg per teasp.

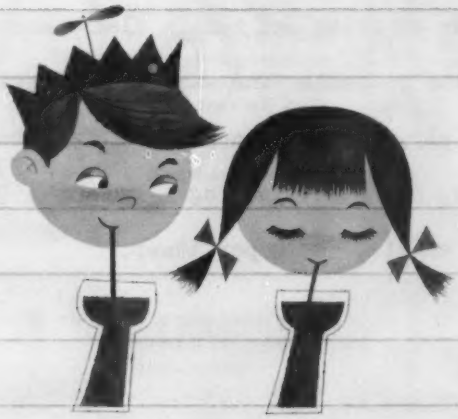
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Original Research
in Medicine and Chemistry

Noludar®—brand of methyprylon (3,3-diethyl-5-methyl-2,4-piperidinedione)

It's a date—

...among other things...which distinguishes Vi-Penta Drops 'Roche.' Since all multivitamin solutions tend to lose strength in time, Vi-Penta® Drops are dated to assure full label potency. Just 0.6 cc daily provides required amounts of A, C, D and B vitamins (including B_6), and you'll find that both mothers and youngsters like them because they're easy to give and easy to take.

Hoffmann - La Roche Inc • Nutley 10 • N. J.



because
your allergic patients
need a lift
a new Rx...



Plimasin®

(tripelennamine hydrochloride and methyl-phenidylacetate CIBA)

new, mild stimulant
and antihistamine

boost their spirits... relieve their allergic symptoms

So often the allergic patient is tired, irritable, depressed—mentally and physically debilitated. Frequently, antihistaminic agents themselves are sedative, adding to this already fatigued and disconsolate state.

Plimasin, because it combines a proved antihistamine with a new, mild psychomotor stimulant, overcomes depression and fatigue while it achieves *potent* antiallergic effects. Its new stimulant component—Ritalin—is totally different from amphetamine: smoother, gentler in action, devoid of pressor effect.



DOSAGE: *One or 2 tablets as required.*

Each Plimasin tablet contains 25 mg. Pyribenzamine® hydrochloride (tripelennamine hydrochloride CIBA) and 5.0 mg. Ritalin® (methyl-phenidylacetate CIBA).

CIBA SUMMIT, N. J.

2/21214

Bentyl
especially
when other antispasmodics have failed

204 OF 240 PATIENTS GET "GRATIFYING TO COMPLETE" RELIEF[1-3]

240 PATIENTS — in three separate groups — with a variety of functional disorders, were placed on Bentyl therapy. *Patients selected for treatment with Bentyl had not received satisfactory relief from other antispasmodic drugs.*

204 PATIENTS experienced "gratifying to complete" relief of their symptoms . . . there was virtual freedom from side effects. The consensus of the three clinicians who conducted the individual studies was: "this compound (Bentyl) *compares more than favourably to any other antispasmodic* and it should be included in our therapeutic arsenal."[3]

For **SAFE, EFFECTIVE RELIEF** of nervous gut — prescribe Bentyl, 2 caps. t.i.d.

1. Nash, G.W.: J. M. A. Georgia 40:231-4, 1951. 2. Chamberlain, D.T.: Geriatrics 17:224-8, 1951. 3. Dorsey, L.: Canadian Med. Assn. J. 69:532, 1953.

Rx Information

Bentyl

Bentyl affords direct (musculotropic) and indirect (neurotropic) spasmolytic action. Bentyl provides complete and comfortable relief in smooth muscle spasm; particularly in functional G.I. disorders, in irritable colon, pylorospasm, biliary tract dysfunction and spastic constipation.

Composition:
Each capsule or teaspoonful (5 cc.) contains 10 mg. of Bentyl (dicyclomine hydrochloride).

Bentyl with Phenobarbital adds 15 mg. of phenobarbital to the preceding formula.

Bentyl Repeat Action with Phenobarbital Tablets contain 10 mg. of Bentyl and 15 mg. of phenobarbital in the outer coating, and 10 mg. of Bentyl in the enteric-coated core.

Dosage:
Adults—2 capsules or 2 teaspoonfuls of syrup, t.i.d. before or after meals. If necessary repeat at bedtime.

Bentyl Repeat Action with Phenobarbital Tablets — 1 or 2 tablets at bedtime, or every eight hours as needed.

In Infant Colic — ½ to 1 teaspoonful, ten to fifteen minutes before each feeding.

Supplied:
Bentyl—In bottles of 100 and 500 blue capsules, and as Bentyl Syrup.

Bentyl with Phenobarbital—In bottles of 100 and 500 blue-and-white capsules, and Bentyl Syrup.

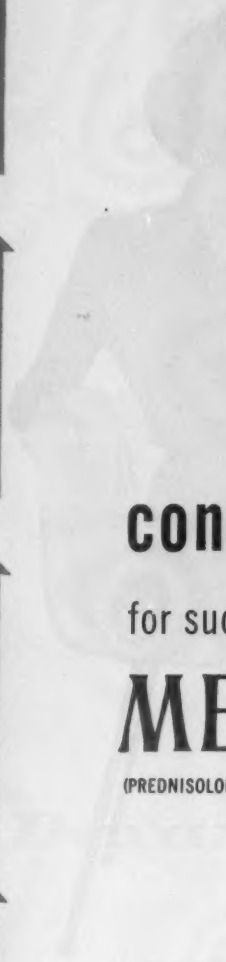
Bentyl Repeat Action with Phenobarbital Tablets—bottles of 100 and 500.

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Since 1828

Another exclusive product of original Merrell research.

T. M. "BENTYL"



in rheumatoid arthritis

continuing benefits

for successful corticosteroid therapy

METICORTELONE*

(PREDNISOLONE)

- therapy usually undisturbed by sodium retention, edema, weight gain
- excellent relief of arthritic pain, swelling, tenderness
- spares patients salt-poor diets
- up to 5 times as potent as hydrocortisone

Available as 1, 2.5, and 5 mg. tablets; 2.5 and 5 mg. capsules

METICORTELONE,* brand of prednisolone. *T. M. ML-J-66-256

Schering

Enriched Bread...

in the Ideal Reducing Diet

In reducing, the primary consideration is the establishment of a negative caloric balance as well as the maintenance of an optimal nutritional state in the obese person. For achieving this objective "the ideal reducing diet . . . not necessarily devoid of any food present in the normal diet" includes "meat, poultry, fish, eggs, milk, and other dairy products, leafy green and yellow vegetables, citrus fruits, and enriched and whole grain products . . . all desirable and necessary" foods.*

High in palatability and high in many nutrients, enriched bread shares notably in helping make the reducing regimen appealing and adequate nutritionally. In so doing it helps "to assure weight reduction without irritability and personality change" as well as "to avoid self defeat due to physical weakness and consequent inactivity."* Furthermore, the "ideal reducing diet" makes for increased likelihood of a permanent change from excessive eating to normal food habits "tuned to self control rather than outright abnegation."

The table presented below shows that 4 to 6 average slices of enriched bread serve to good advantage nutritionally in reducing diets. Providing generous amounts of protein, B vitamins, and minerals, enriched bread goes far toward making the low caloric regimen adequate in these nutrients. Its protein, containing an average of 10.5 per cent of milk protein, functions for growth and repair of tissues as well as for maintenance. Fresh or toasted, or as tasty sandwiches, enriched bread provides eating satisfaction, an essential for making the reducing regimen tolerable.



The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

Contribution of 6 Slices of Enriched Bread

	Nutrients and Calories	Percentages of Allowances**
Protein	11.7 Gm.	18%
Thiamine	0.33 mg.	22
Niacin	3.0 mg.	20
Riboflavin	0.21 mg.	13
Iron	3.3 mg.	28
Calcium (average)	122 mg.	15
Calories	379	13

*Berryman, G. H.: Obesity—A Brief Review of the Problem, Metabolism 3:544 (Nov.) 1954.

**Percentages of daily allowances for fairly active man 45 years of age, 67 inches in height, and weighing 143 pounds: Recommended Dietary Allowances, Washington, D.C., National Academy of Sciences—National Research Council Publication 302, 1953.

AMERICAN BAKERS ASSOCIATION 20 North Wacker Drive • Chicago 6, Illinois



for the patient who is "tired all the time"

Many of your patients may complain of a "tiredness" that has destroyed their ability to think and has taken from them all the purpose, the fun, and the flavor of living. Rest does not help—for this is not fatigue due to overexertion, but *psychogenic fatigue*, a result of monotonous routine, overworry, or frustrating circumstances.

With 'Dexamyl', you can help many of the patients with this common and unnerving condition. The unique mood effect of 'Dexamyl' subtly replaces anxiety and depression with a renewed sense of cheerfulness, confidence and optimism—*thereby restoring the ability to think and work.*

Dexamyl* *tablets • elixir • Spansule† capsules*

Each 'Dexamyl' Tablet and each teaspoonful (5 cc.) of the Elixir contains: Dexedrine* Sulfate (dextroamphetamine sulfate, S.K.F.), 5 mg.; and amobarbital, ½ gr.

Also Available: 'Dexamyl' *Spansule* (No. 1), slowly releasing the equivalent of *two* tablets; 'Dexamyl' *Spansule* (No. 2), slowly releasing the equivalent of *three* tablets.

Smith, Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

†T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

Patent Applied For.

Full Diuretic Control with Fewer Injections

The THIOMERIN program combines parenteral and suppository therapy to solve a major diuretic problem—drastic diuresis, patient alternately dry and waterlogged.

Parenteral THIOMERIN initiates diuresis . . . supplemented by THIOMERIN Suppositories to permit maximal spread between injections, to prevent fluid accumulation, and to maintain dry weight. Together, they offer a well-tolerated and convenient regimen for smooth edema control.[1]

Supplied: THIOMERIN Suppositories, boxes of 12. Injection THIOMERIN Solution, vials of 2 cc., boxes of 12; vials of 10 cc. Injection THIOMERIN (lyophilized), vials of 1.4 Gm. (10 cc. upon reconstitution) and 4.2 Gm. (30 cc. upon reconstitution).

1. Daly, J.W.: Am. J. M. Sc. *228*:440 (Oct.) 1954.

INJECTION RECTAL SUPPOSITORIES

THIOMERIN® Sodium

MERCAPTOMERIN SODIUM





for the "Sippy-diet" patient

a welcome *(and often necessary)* change from "milk-and-cream"

MULL-SOY® Powdered

Pioneer soy alternative to milk... reported to be "noticeably more soothing to the upper gastrointestinal tract and seemingly easier to digest."[1] Comparable to milk in buffering[2] and nutritional[3] qualities. Contains no cholesterol... and costs the patient *much* less than milk-and-cream. Easy to prepare—4 level tablespoonfuls to 8 oz. water. In 1-lb. tins at all drug outlets.

1. Balfour, D. C., Jr.: Am. J. Gastroenterol. 22:181, 1954. 2. Burke, J. O., et al.: Internat. Rec. Med. & Gen. Practice Clin. 167:587, 1954. 3. Sternberg, S. D., and Greenblatt, I. J.: Ann. Allergy 9:190, 1951.

Are you wondering how MULL-SOY Powdered tastes? Return this coupon for professional trial samples and see for yourself how *pleasant* it can be for your milk-weary or milk-intolerant ulcer patients.

THE BORDEN COMPANY
Prescription Products Division, Dept. 203
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Please send to me, without charge, four 4-oz. tins of MULL-SOY Powdered.

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Sustagen®

Therapeutic Food For Complete Nourishment

Sustagen is the only therapeutic food which contains all known nutritional essentials: protein, carbohydrate, fat, vitamins and minerals. It may be used as the only source of food or to fortify the diet in brief or prolonged illness.

SUSTAGEN

repairs tissue
restores appetite
overcomes asthenia
in
cirrhosis
peptic ulcer
geriatrics
infections
trauma
chronic disease

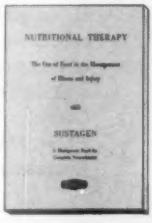
Sustagen is the right kind of food for many conditions

Sustagen was designed to meet many physical and biochemical requirements of therapeutic nutrition. Thus Sustagen may be used by mouth or by tube as the only source of food or to fortify the therapeutic diet.

Type of Diet*	Amount of Sustagen	Calories	Protein Gm.	Carbohydrate Gm.	Fat Gm.	Comment
Low purine diet	Sustagen, 530 Gm.	2050	124	350	19	no purine nitrogen; 42 mg. uric acid
Low cholesterol diet	Sustagen, 530 Gm.	2050	124	350	19	150 mg. cholesterol
High protein, low fat diet	Sustagen, 580 Gm.	2250	137	385	20	contains all amino acids in well balanced amounts
Liquid diet	Sustagen, 540 Gm.	2100	127	360	19	viscosity suitable for tube feeding
Bland diet (peptic ulcer)	Sustagen, 570 Gm.	2200	134	377	20	buffering capacity of Sustagen is effective and prolonged
Liberalized low sodium diet†	Sustagen, 465 Gm.	1800	110	310	16	980 mg. sodium

†Note that the sodium content of Sustagen limits its use when dietary restriction of sodium must be severe.

*Selected from "The Use of Food in the Management of Illness and Injury." This booklet contains information on the composition and uses of Sustagen in a variety of conditions. It may be obtained from your Mead Representative or from the Medical Department.



Sustagen is supplied in powder form in 1 pound, 2½ pound and 5 pound cans. Only water need be added to provide a smooth, palatable liquid. One pound provides 1750 calories, including 105 Gm. protein.

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MEAD JOHNSON & COMPANY • EVANSVILLE 21, INDIANA, U.S.A.

....."the right kind of food"....

"The primary driving force of all animals is the necessity of finding the right kind of food and enough of it."[1] To Elton's observation it may be added that for optimal health *the right kind of food* must be available continuously and that food *enough for maintenance* may be inadequate to meet the increased needs of illness.

Elton's criteria are particularly appropriate in illness. They immediately reveal the dilemma of nutritional therapy: needs are increased at a time when the appetite and the ability to eat are often severely impaired. Further, physiologic disturbances may require the restriction of certain nutrients (sodium, cholesterol, fat) present in many common foods. Thus, in illness, selection of *enough of the right kind of food* imposes difficult problems.

Food for use in therapy should, of course, contain all essential nutrients. Amounts should be suitable to maintain life and provide for needs increased by disease or injury. The caloric density, tolerability and palatability of foods must also be kept in mind if adequate nourishment is to be provided and if anorexia, nausea, diarrhea or sensitivity are to be avoided.

Sustagen provides maximal nutritional support, with minimal problems of tolerance. Sustagen is *the right kind of food* for sick patients.

1. Charles Elton, Animal Ecology, Sidgwick and Jackson, London, 1935.

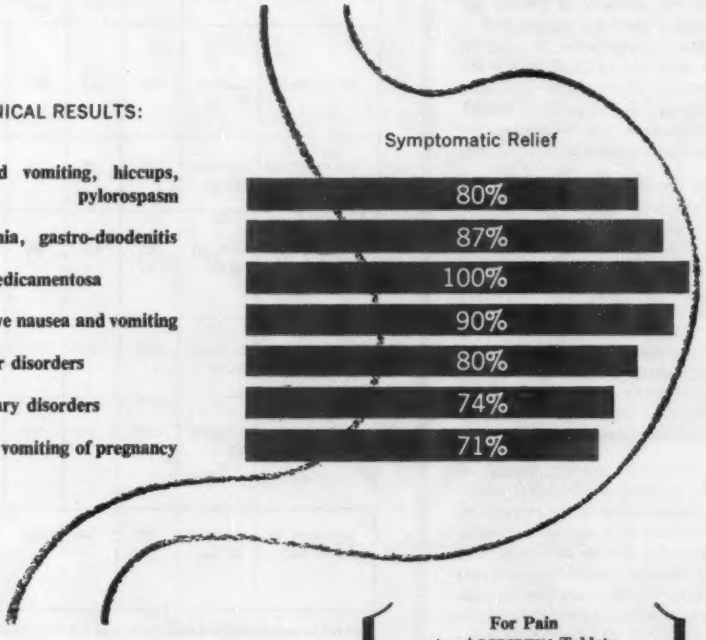
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(procaine isobutyrate, RORER)

for direct, topical management of

nausea . . . vomiting . . . gastritis

* CLINICAL RESULTS:



Given orally, in capsules or elixir, PROBUTYLIN effectively relieves gastrointestinal symptoms of many disorders by direct, topical anesthetic action on the mucosa and muscularis. *Supplied:* Capsules PROBUTYLIN, 300 mg., bottles of 50. Elixir PROBUTYLIN, 10%, bottles of 180 cc. Literature and samples forwarded on request.

For Pain
try ASCRIPTIN Tablets
(Aspirin buffered with MAALOX)

- Doubles blood salicylate level
- Action more prolonged
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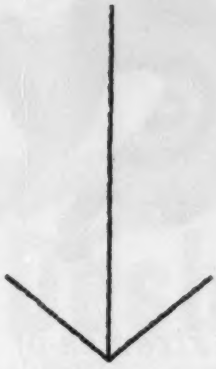
Samples on request

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PHILADELPHIA, PA.



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Cough
suppressant
effect

Ten milligrams of Romilar equal
fifteen milligrams of codeine.
Yet Romilar is non-narcotic -
does not cause nausea, constipation,
drowsiness, or addiction.
Tablets; Syrup; Expectorant (with
Ammonium Hydrochloride).

Romilar® Hydrobromide - brand of dextromethorphan hydrobromide

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To counteract extremes of emotion



Desbutal®

(DESOXYN® *plus* NEMBUTAL®)

DESBUTAL gives the disturbed patient a new sense of well-being and energy, while calming his tensions and anxieties. One capsule represents 5 mg. DESOXYN Hydrochloride (Methamphetamine Hydrochloride, Abbott), and 30 mg. NEMBUTAL Sodium (Pentobarbital Sodium, Abbott). Bottles of 100 and 1000. Abbott



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In Congestive Heart Failure
R_x 'Wide Safety Margin'
GITALIGIN®

WHITE'S BRAND OF AMORPHOUS GITALIN

Authoritative investigators have reported that the digitalizing dose of Gitaligin is approximately one-third the toxic dose.[1-5]

This "wide margin of safety" (difference between therapeutic and toxic doses) permits rapid digitalization and successful maintenance with a minimum of toxic side reactions—even in refractory cases where other glycosides have failed.[6] And, cost to your patient is no greater than ordinary digitalis preparations.

Supplied: Scored tablets of 0.5 mg. Bottles of 30 and 100.

References: 1. Ehrlich, J. C.: Arizona Med. *12:* 239 (June) 1955. 2. Weiss, A., and Steigmann, F.: Am. J. M. Sc. *227:* 188 (Feb.) 1954. 3. Dimitroff, S. P.; Griffith, G. C.; Thorner, M. C., and Walker, J.: Ann. Int. Med. *39:* 1189 (Dec.) 1953. 4. Hejtmancik, M. R., and Herrmann, G. R.: Texas St. J. M. *51:* 238 (May) 1955. 5. Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation *5:* 201 (Feb.) 1952. 6. Denham, R. M.: J. Kentucky St. M. Assoc. *53:* 209 (Mar.) 1955.

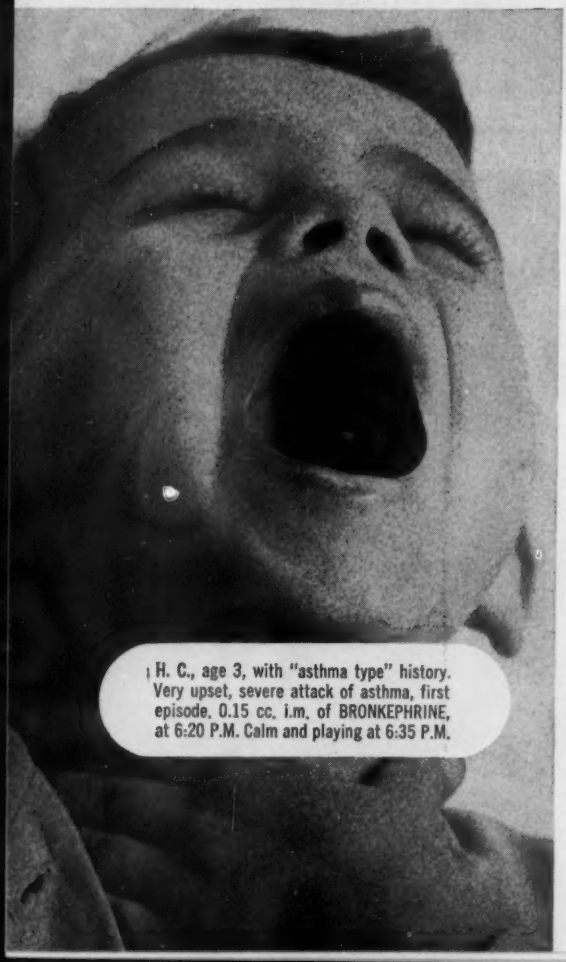
It's so easy to switch to 'wide safety margin' Gitaligin. Follow these simple dosage equivalents wherever digitalis therapy is indicated.

DIGITALIS PREPARATION	AVERAGE DAILY MAINTENANCE DOSE	GITALIGIN DOSAGE EQUIVALENT (APPROX.)
Digitalis leaf	0.1 Gm.	0.5 mg.
Digitoxin	0.1 mg.	0.5 mg.
Digoxin	0.5 mg.	0.5 mg.

WHITE LABORATORIES, INC. Kenilworth, N. J.

Fright, as well as anoxia, grasps the classical "first-attack" asthmatic child. You well know that this youngster needs air and reassurance. Both are available with BRONKEPHRINE without side effects subtracting from success. BRONKEPHRINE's lack of excitation,[1,2,3] in fact, far less than epinephrine,[3] has been particularly valuable in the control of asthma in children.[1] This can be true in your practice, too. BRONKEPHRINE's lack of excitation is reflected by another happy advantage—lack of pressor effect.[1,3-6] Even hypertensive asthmatics can now receive *potent* antiasthmatic therapy without affecting their blood pressure—a factor of major importance in selecting asthma therapy—whether the patient is hypertensive or not.

air and reassurance



H. C., age 3, with "asthma type" history. Very upset, severe attack of asthma, first episode. 0.15 cc. i.m. of BRONKEPHRINE, at 6:20 P.M. Calm and playing at 6:35 P.M.

But this potent drug, "... a superior tool for the treatment of bronchial asthma,"[1] unlike other effective sympathomimetic amines, develops tolerance far less frequently and to a lesser degree—an obvious advantage in the prolonged treatment of asthma.[1]

BRONKEPHRINE (ethylnorepinephrine Breon) for either intramuscular or intravenous injection—your drug of choice for *any* asthmatic—is available in 10 cc. multidose vials, containing 2 mg. of BRONKEPHRINE in each cc.

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another exclusive, quality-controlled parenteral from Breon, your House of Advanced Office Parenteral Medication.

We will be pleased to send you more information, or a clinical sample for your practice. GEORGE A. BREON & COMPANY
1450 Broadway, New York 18, N. Y.

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Breon

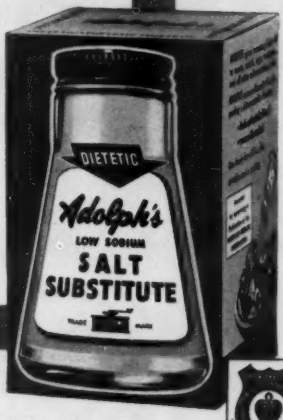
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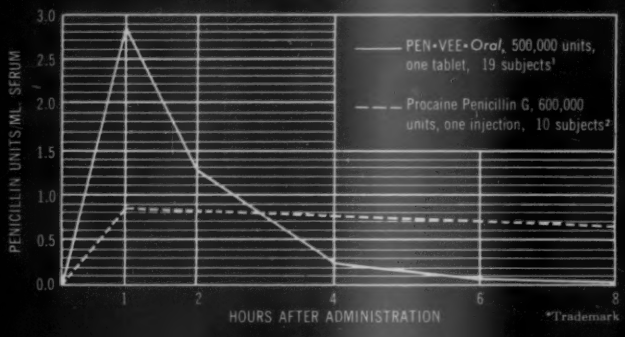
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Iodide
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Tablets 25 mg.

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For the medical management of peptic ulcer, hypertrophic gastritis and intestinal hypermotility.

Notably effective in relieving pain due to smooth muscle spasm.

In usual dosage, undesirable side effects are rare.

Also available with added phenobarbital, 15 mg.

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BRAND OF OXYTETRACYCLINE

...well-tolerated, rapidly effective broad-spectrum antibiotic of choice.

Capsules, tablets, taste-tempting liquid forms and special preparations for parenteral, topical and ophthalmic use.

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Local Youngsters In Child's Dream Birthday Party

Sharing the same birthday, seven children from the Magnolia Hollow section were yesterday given a joint party by Mrs. James Robb, Jr.

Dressed dolls, Davy Crockett caps, and games vied with refreshments for the children's attention.

"Each child," said Mrs. Robb, "was given ham salad sandwiches, potato salad and a choice of pastries."

Diarrhea... the uninvited guest

To combat susceptible infectious forms, STREPTOMAGMA combines potent antibacterial, adsorptive, and protective actions. Soothes the bowel, encourages formation of normal stools. For routine management in other forms of diarrhea, prescribe KALPEC®—pectin with kaolin in alumina gel.

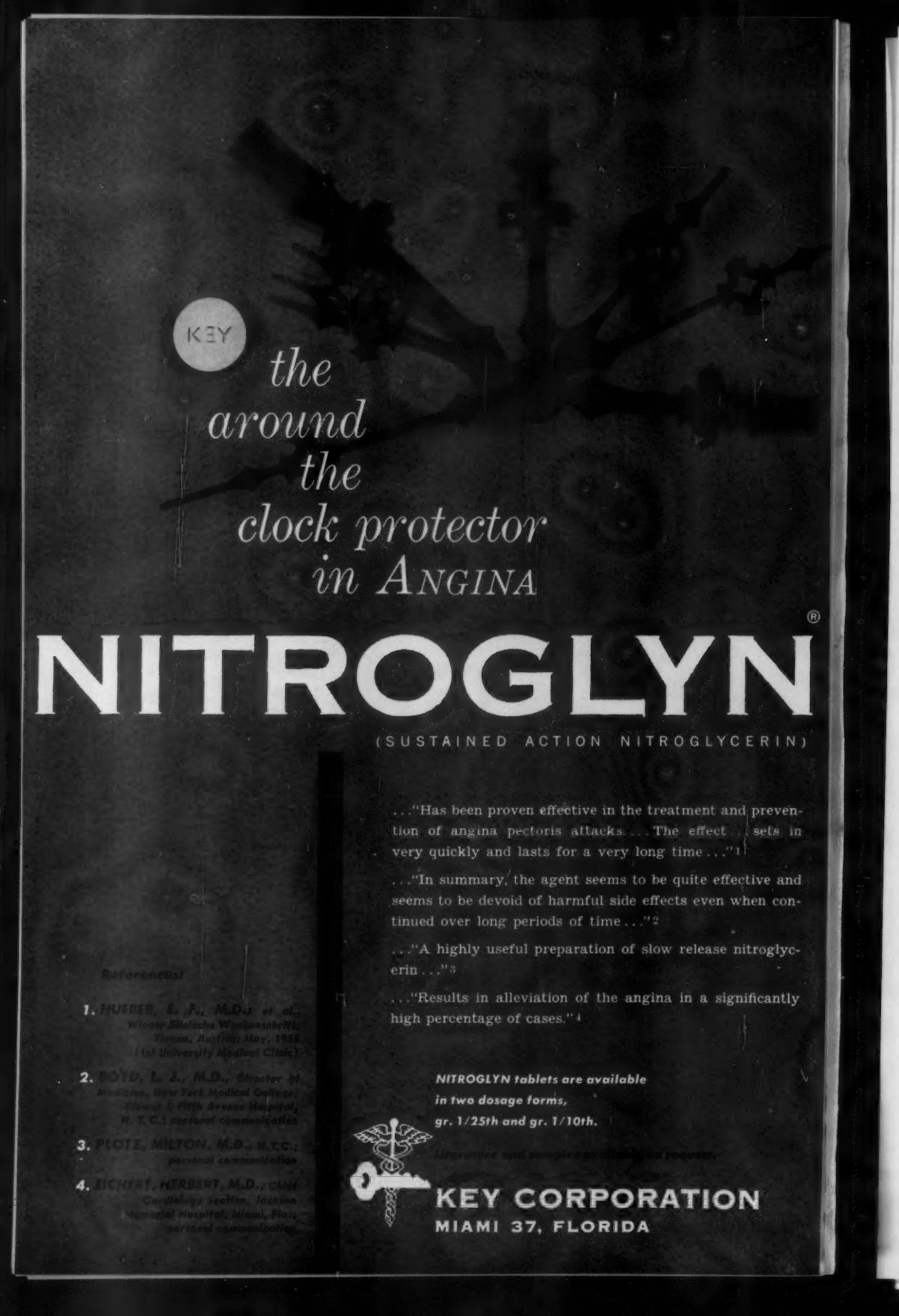




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Dihydrostreptomycin Sulfate and Pectin with Kaolin in Alumina Gel

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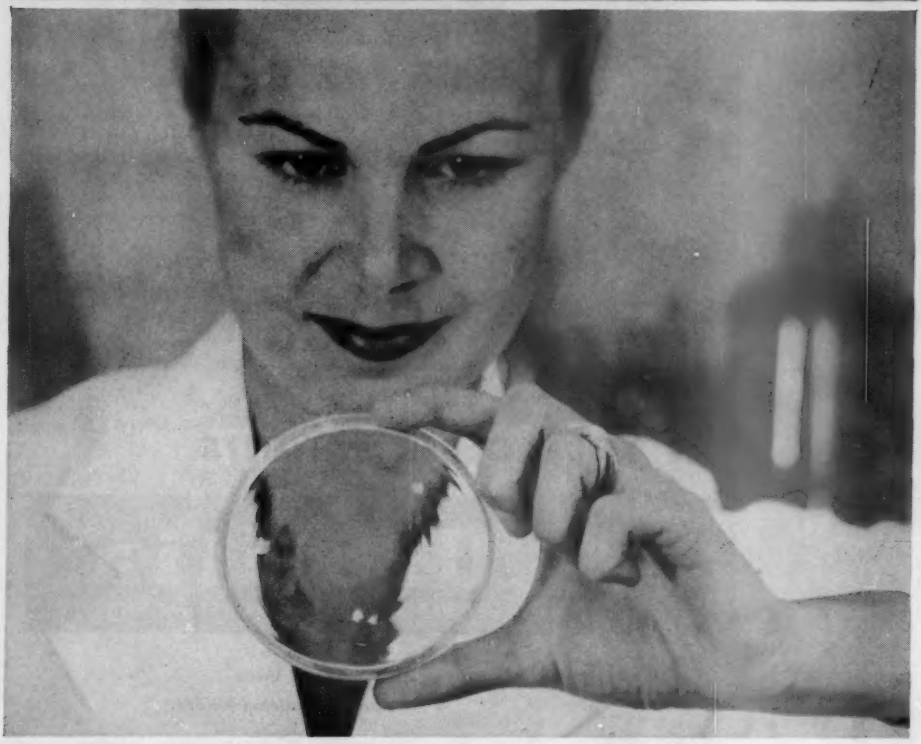

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the
around
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in ANGINA
NITROGLYN®
(SUSTAINED ACTION NITROGLYCERIN)
..."Has been proven effective in the treatment and prevention of angina pectoris attacks... The effect ... sets in very quickly and lasts for a very long time..."[1]
..."In summary, the agent seems to be quite effective and seems to be devoid of harmful side effects even when continued over long periods of time..."[2]
..."A highly useful preparation of slow release nitroglycerin..."[3]
..."Results in alleviation of the angina in a significantly high percentage of cases."[4]
References:
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4. EICHERT, HERBERT, M.D.; Chief Cardiology Section, Jackson Memorial Hospital, Miami, Fla.; personal communication.
NITROGLYN tablets are available in two dosage forms, gr. 1/25th and gr. 1/10th.
Literature and samples available on request.
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Sulfathalidine®

PHTHALYLSULFATHIAZOLE

a reliably effective adjunct to intestinal surgery

MAJOR ADVANTAGES: Suppresses intestinal bacterial growth.[1] Minimum systemic absorption[2] insures maximum local effect. Effective doses well tolerated, economical.



SULFATHALIDINE, given before and after bowel surgery, is nontoxic and assures effective suppression of bacterial growth, even when there is watery diarrhea.

SULFATHALIDINE allows for preoperative mechanical preparation of the colon, favors early healing, and reduces the incidence of peritonitis. It's also a useful adjunct in ulcerative colitis. The *dosage* depends on body weight. The average adult dose of SULFATHALIDINE is 8 to 12 tablets (each 0.5 *Gm.*) daily in divided doses.

'Sulfathalidine' can also be given as the pleasantly-flavored suspension, CREMOTHALIDINE®, each oz. containing 6.0 *Gm.* of 'Sulfathalidine.'

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Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

References: 1. N.N.R. 1954, p. 107. 2. Poth, E. J., J.A.M.A. *153*:1516, December 26, 1953.



GOOD FOR GRANDMA, TOO!

Borcherdt

MALT SOUP Extract*

A New Dietary Management for

CONSTIPATED ELDERLY

A bowel content modifier that softens dry, hard stools by dietary means without side effects.[1] Acts by promoting an abundant fermentative bacteria in the colon, thus producing soft, easily evacuated stools. Retards growth of putrefactive organisms. By maintaining a favorable intestinal flora, Malt Soup Extract provides *corrective therapy for the colon, too!*

DOSE: 2 tablespoonfuls b.i.d. until stools are soft (may take several days), then 1 or 2 Tbs. at bedtime.

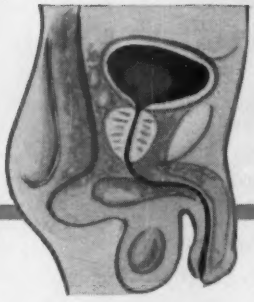
*Specially processed malt extract neutralized with potassium carbonate. In 8 oz. and 16 oz. bottles.

1. Cass, L. J. and Frederik, W. S.: Malt Soup Extract as a Bowel Content Modifier in Geriatric Constipation, Journal-Lancet, 73:414 (Oct.) 1953.

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BORCHERDT MALT EXTRACT CO.
217 N. Wolcott Ave. • Chicago 12, Ill.

RELIEVES PAINFUL URINATION IN YOUR OLDER PATIENTS



Urolitia

NON-TOXIC, SOOTHING URINARY ANTISEPTIC

- **Clears Infected Urine**
- **Soothes the Irritated Bladder**

When the problem is chronic urinary infection, especially in older patients—Urolitia is the specific answer.

Urolitia clears infected urine promptly while it soothes the irritated bladder. It permits high methenamine dosage—up to 120 grains per day when necessary—to provide bacteriostasis. Effective against E. coli, S. albus, S. aureus. Provides the soothing action of triticum and zea. May be given repeatedly over long periods without toxicity, drug fastness or side reactions.

DOSE: One Tbs. in half cup warm water, q.i.d. ½ hr. a.c. and h.s. Decrease dose after second day.

RESIDUAL URINE

Residual urine due to cystocele or hypertrophied prostate means chronic, frequent re-infection. Because Urolitia soothes the bladder, and can be given repeatedly over long periods, it maintains bacteriostasis and freedom from symptoms in these conditions.

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PROTOVERATRINES A AND B WITH RESERPINE



IN MANY OF YOUR HYPERTENSIVE PATIENTS, conservative treatment with reserpine can be made more effective by placing the patient on safe combination therapy.

EFFECTIVE. When combined with reserpine, the blood pressure lowering effects of protoveratrines A and B can be achieved with smaller dosage, and with marked decrease in annoying side actions.

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ACCURATE. Veralba/R potency is precisely defined by chemical assay. All active ingredients are in purified, crystalline form.

Each Veralba/R tablet contains 0.4 mg. of protoveratrines and 0.08 mg. of reserpine. Bottles of 100 and 1000 scored tablets.

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in biliary tract disorders

CHOLOGRAFIN

intravenously provides more diagnostic information than oral contrast media

More consistently than oral contrast media, intravenous Cholografin visualizes the entire extrahepatic biliary system. It does this "whether or not the gallbladder functions or is even present."[1]

After cholecystectomy, moderate to severe symptoms may persist in 10 to 25 per cent of patients whose gallbladders are removed because of cholelithiasis, and in 50 per cent of those whose gallbladders are removed for so-called noncalculous gallbladder disease.[2] In these patients, Cholografin may reveal strictures, calculi in the common or hepatic ducts, or cystic duct remnants. It may also reveal dilatation of the common duct (presumptive evidence of dyskinesia or organic obstruction).

Preoperative visualization of the gallbladder and extrahepatic ducts, even when the gallbladder is not functioning, means that Cholografin can frequently reveal radiolucent calculi in the gallbladder, hepatic and common ducts. It can also reveal anomalies and be of diagnostic value when neoplasm is suspected. Biliary surgery can now be based on more complete diagnostic information than can be provided by oral media.

Cholografin, Squibb iodipamide, is available as *Cholografin Sodium*, in cartons of two 20-ml. ampuls with two 1-ml. ampuls for sensitivity testing, and *Cholografin Methylglucamine*, in cartons containing one 20-ml. ampul with one 1-ml. ampul for sensitivity testing.

SQUIBB

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Salicylates again endorsed for rheumatoid arthritis

New evidence on the comparative effectiveness of acetylsalicylic acid and cortisone in rheumatoid arthritis reveals that the progress of patients on salicylates is comparable to progress on cortisone. And a recent survey of members of the American Rheumatism Association indicates overwhelming preference for salicylates.

Modern salicylate therapy at its best

Pabirin combines acetylsalicylic acid with PABA to achieve *high* salicylate blood levels with *low* dosage. Vitamin C (300 mg.) in a daily dosage of 6 capsules helps counteract depletion in salicylate therapy. Pabirin stops pain fast; it is a rapidly disintegrating capsule, not an enteric-coated tablet.

No adrenal atrophy, electrolyte imbalance

Pabirin circumvents the potential hazards of steroid therapy, such as adrenal atrophy, while being equally effective. It contains neither sodium nor potassium, an advantage when either of these electrolytes must be restricted.

Bibliography:
Joint Committee of the Medical Research Council and Nuffield Foundation: Brit. M. J. *2*:695 (Sept. 17) 1955.
Editorial: Brit. M. J. *2*:725 (Sept. 17) 1955.
Lowman, E. W., and others: GP *12*:69 (Nov.) 1955.

Each capsule contains:

Acetylsalicylic acid	(5 gr.) 300 mg.
Para-aminobenzoic acid	(5 gr.) 300 mg.
Ascorbic acid	50 mg.

Average dose: 2 to 3 capsules 3 or 4 times daily.

Supplied: In bottles of 100, 500 and 1,000.

Smith-Dorsey • Lincoln, Nebraska
a division of The Wander Company



Pabirin®

safest fast-acting salicylate-PABA combination

to NORMALIZE, use KONSYL®

It is important, when inducing normal bowel function, to supply a non-irriating bulk to the colon, especially in those cases in which it has been necessary to eliminate from the diet the high roughage foods containing irritating bulk (lignin and cellulose).

It has been shown[1] that the colon resumes a more normal peristaltic pattern[2] when it is supplied with a stool of medium soft consistency of sufficient bulk[3], especially if the indigestible portion of that bulk consists primarily of hemicellulose[4].

KONSYL is a vegetable concentrate of naturally occurring hemicelluloses. It is derived from blond psyllium seed and provides just the moist, smooth, effective bulk so essential to normal peristalsis. Its use has been shown to materially hasten the rate of improvement in patients with the irritable colon syndrome[5]. KONSYL contains 100% bulk producing material.

Furthermore, Konsyl is available in 6-ounce and 12-ounce containers at significantly lower-cost-to-patient prices. That's why we say

to NORMALIZE, use KONSYL®

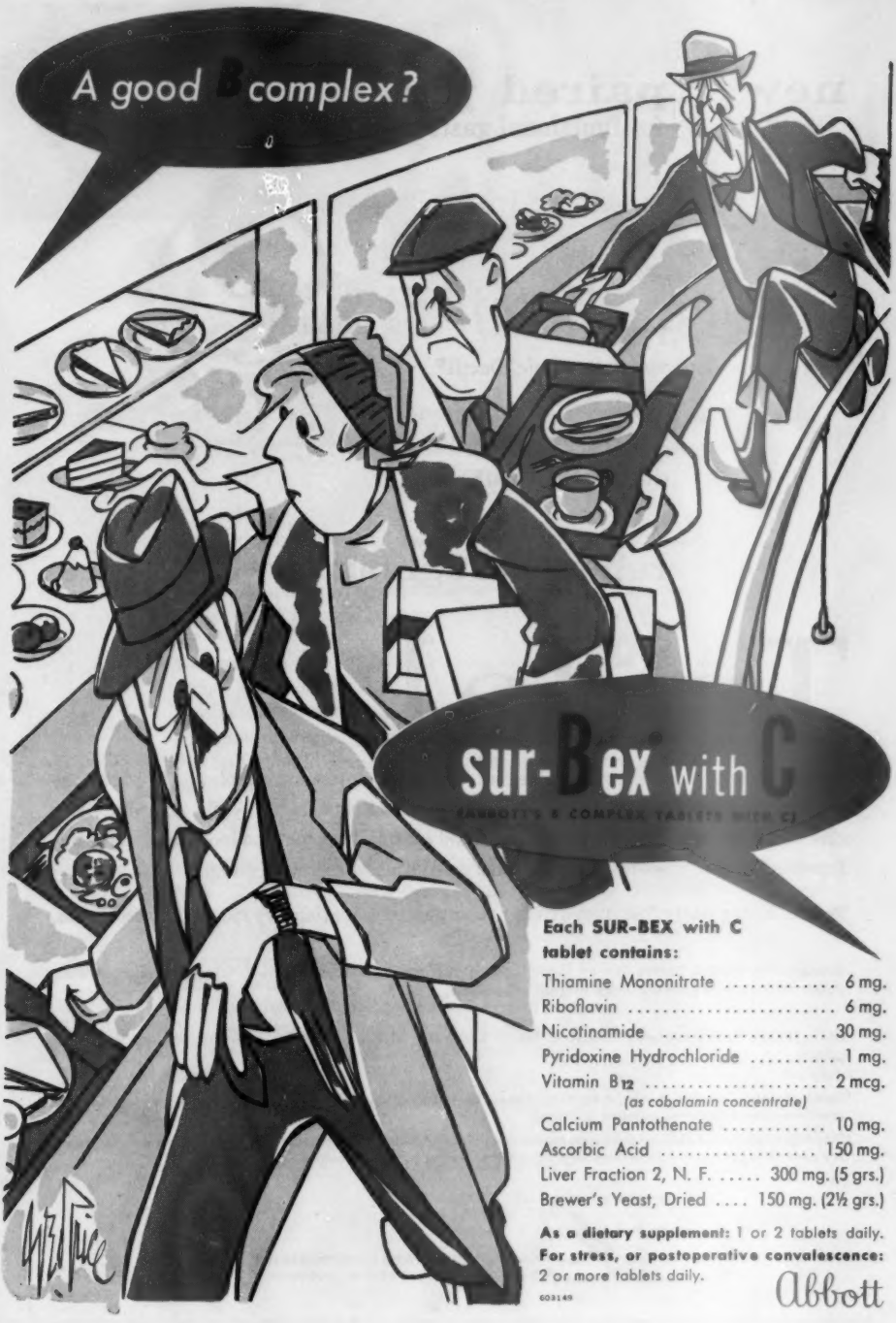
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Each SUR-BEX with C tablet contains:

Thiamine Mononitrate	6 mg.
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Nicotinamide	30 mg.
Pyridoxine Hydrochloride	1 mg.
Vitamin B_{12} *(as cobalamin concentrate)*	2 mcg.
Calcium Pantothenate	10 mg.
Ascorbic Acid	150 mg.
Liver Fraction 2, N. F.	300 mg. (5 grs.)
Brewer's Yeast, Dried	150 mg. (2½ grs.)

As a dietary supplement: 1 or 2 tablets daily.
For stress, or postoperative convalescence: 2 or more tablets daily.

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new... paired piperidol action
for functional gastrointestinal complaints



rapid
visceral eutonic, Dactil*

prolonged
cholinolytic, Piptal†

relief throughout the G. I. tract

Tridal

TRIDAL permits more comprehensive control of gastrointestinal complaints by providing the combined benefits of two piperidols. The local action of Dactil* works immediately to give **rapid** relief of gastrointestinal pain and spasm; the potent cholinolytic Piptal† reinforces relief and provides **prolonged** normalization of secretion and motility.

TRIDAL is singularly free from urinary retention, constipation, dry mouth, blurred vision.

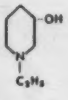
dosage: One TRIDAL Tablet two or three times a day and at bedtime. Unless rapidly swallowed with water, TRIDAL will produce some lingual anesthesia.

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THE URINARY EXCRETION TEST IN THE DIAGNOSIS OF ADDISONIAN PERNICIOUS ANEMIA *

By S. FRED RABINER, M.D., HERBERT C. LICHTMAN, M.D., JACQUELINE MESSITE, M.D., R. JANET WATSON, M.D., F.A.C.P., VICTOR GINSBERG, M.D., F.A.C.P., *Brooklyn, New York,* LEON ELLENBOGEN, Ph.D., and WILLIAM L. WILLIAMS, Ph.D., *Pearl River, New York*

ADDISONIAN pernicious anemia is a deficiency disease resulting from the lack of a specific gastric secretion which is essential for the optimal absorption in the intestine of orally ingested vitamin B_{12}. Probably a mucoprotein,[1, 2] this gastric enzyme, commonly referred to as intrinsic factor,[3, 4] is produced by the mucosal cells of the stomach of man and other animals. It has not yet been fully characterized chemically, nor is there available a direct method for detecting its presence in the stomach secretions.

In hematologic relapse the diagnosis of pernicious anemia is readily established by the findings of megaloblastic erythropoiesis, macrocytic normochromic anemia, leukopenia, gastric achlorhydria, with or without the neurologic evidences of combined system disease. Treatment with vitamin B_{12} or liver extract induces a complete hematologic remission, and this form of treatment is continuously required throughout the patient's life. Without a knowledge of the hematologic findings prior to treatment, it is extremely difficult to establish a diagnosis of pernicious anemia after the blood counts have returned to normal levels or the bone marrow has been converted to a normoblastic appearance. At this time the diagnosis depends upon the demonstration of the absence of intrinsic factor activity in the patient's gastric juice.

Until recently the only known method for measuring the intrinsic factor activity of a specimen of gastric juice [4] was to feed, each day, about 50 ml.

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of this material, properly neutralized and filtered, plus an otherwise ineffectual quantity of vitamin B_{12}, to another patient with addisonian pernicious anemia in hematologic relapse. The presence or absence of intrinsic factor activity in the gastric juice administered was determined by the degree of reticulocytosis and erythrocyte regeneration induced in the recipient patient. This cumbersome and time-consuming procedure is too impractical for routine use, and has been employed only rarely as an investigative tool.

Schilling [5] demonstrated that normal persons will excrete in their urine a significant fraction of the radioactivity of an orally administered dose of vitamin B_{12} tagged with radioactive cobalt (Co^{60}). This would occur only

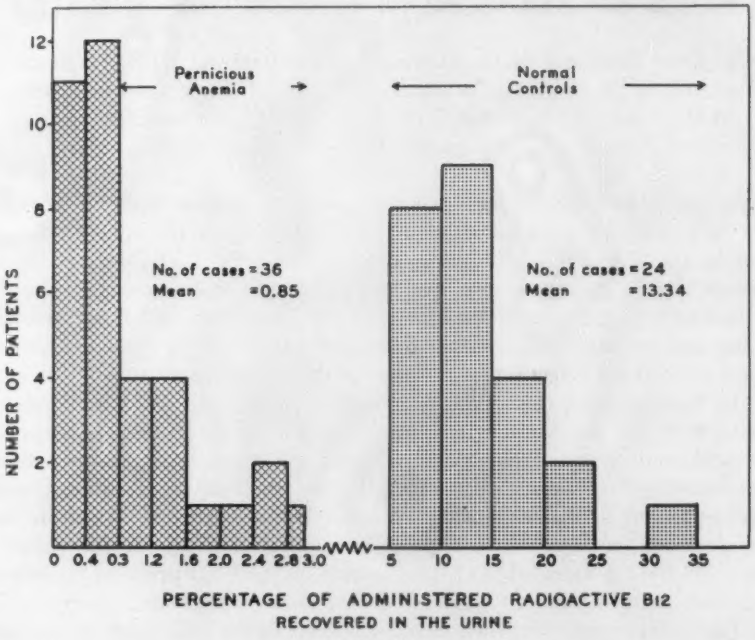


FIG. 1.

if a very large, parenterally administered dose of non-radioactive vitamin B_{12} was given shortly afterwards, as a "flushing" dose. Patients with pernicious anemia, however, excreted negligible amounts of the radioactivity on the same regimen unless a potent source of intrinsic factor was given with the oral vitamin B_{12}.

This observation has been successfully applied as a urinary excretion test to determine the presence or absence of naturally occurring intrinsic factor in order to establish the diagnosis of addisonian pernicious anemia, especially in non-anemic individuals.

It is the purpose of this report to relate our experiences with the urinary excretion test as a diagnostic procedure for addisonian pernicious anemia in hematologic remission.

Methods

The individuals studied in this series include normal laboratory personnel, patients hospitalized for a variety of reasons not including pernicious anemia, and patients with pernicious anemia in remission. All of the usual criteria for the diagnosis of addisonian pernicious anemia were satisfied in the last group.

A urinary excretion test similar to that described previously [5] was performed on each subject. During the course of the study modifications [6, 7] were made in the original method to improve its accuracy and thereby the validity of our interpretations.

Table 1

General Outline of Method

Day	Oral $B_{12}Co^{60*}$	Intramuscular Vitamin B_{12}	Intrinsic Factor	
	Micrograms			
1	0	0	0	Control for urine radioactivity
2	2	1000	0	Test for endogenous intrinsic factor
3	0	1000	0	Extra "flush"
4	2	1000	Known potent preparation	Test of "maximal" excretion

* Specific activity, 0.25 μc./μg.

The procedure employed is outlined in table 1. The total urinary output was collected daily. After the volume had been recorded, the radioactivity of an aliquot was determined, using a well type scintillation counter. When the subject was not hospitalized, urine samples were collected at home and brought to the laboratory each morning. The urine collected on the first day served as a control. This step proved its value in one instance when the control sample was found to be radioactive as a result of a previously administered dose of I^{131} given without our knowledge. On the second day the test subject received 2 μg of vitamin B_{12} Co^{60} (containing approximately 0.5 microcuries of Co^{60}), administered orally before breakfast. Simultaneously he received an intramuscular injection containing 1,000 μg of non-radioactive vitamin B_{12} (the "flushing dose").

On the third day another injection of 1,000 micrograms of vitamin B_{12} was given intramuscularly (the "extra flush"). The last two days of the test were utilized as a guide to the maximal excretion capacity of the patient for radioactive vitamin B_{12}. Therefore, in addition to the administration orally of vitamin B_{12} Co^{60} and the intramuscular, non-radioactive B_{12}, a

sample of intrinsic factor extract of known potency * was given orally. The dose of intrinsic factor used for the urinary excretion test was several times greater than that required for optimal erythrocyte regeneration, as was demonstrated previously, when this substance was used in clinical assay on patients with addisonian pernicious anemia in relapse. This was followed, on the last day, by the intramuscular injection of 1,000 μg of non-radioactive vitamin B_{12}.

For diagnostic purposes, therefore, the test required four days of complete urine collection, with a random sample of urine collected just prior to beginning. Two doses of radioactive vitamin B_{12} are given, totaling 1.0 microcurie of Co^{60}.

Results

The urinary excretion of radioactive vitamin B_{12} in 36 patients with addisonian pernicious anemia was less than 3.0% of the orally administered dose in each instance. The mean for the group was 0.85%, with a range

Table 2

	Number of Patients	Percentage of Administered ($B_{12}Co^{60}$) Radioactivity Recovered in Urine	
		Mean	Range
Controls	24	13.3	5.0–34.2
Addisonian pernicious anemia	36	0.85	0.5– 3.0
Addisonian pernicious anemia given intrinsic factor	33	8.2	1.8–19.2

of 0.05 to 3.0%. Twenty-four normal adults had a mean excretion of 13.3%, the range being 5.0 to 34.2% (table 2). Note that there is no overlap in the results in these two groups of patients (table 2 and figure 1).

In preliminary studies on normal individuals urine was collected for only 24 hours after an oral dose of radioactive vitamin B_{12}, as originally described by Schilling.[5] To determine whether there was any residual excretable radioactivity on subsequent days, repeated flushing doses of 1,000 μg of non-radioactive vitamin B_{12} were parenterally administered. The results of this study are illustrated in table 3. It can be seen that significant quantities of radioactivity appeared in the urine on the second day, and in some instances on the third day as well. In one presumably normal individual (R. B.) the amount of administered radioactivity excreted in the urine in the first 24 hours was equivalent to only 2.4%. In a second 24 hour collection period he excreted another 2.6%, bringing the total to 5%.

Repeated flushing doses were administered to patients with pernicious

* This material was prepared at the Lederle Laboratories, Pearl River, N. Y.

TABLE 3

Effect of Repeated Flushing Injections
Control Subjects

Pt.	Urine Radioactivity %			
	Day 1	Day 2	Day 3	Total
W. L. W.	10.5	8.6	2.9	22.0
J. G.	15.9	6.7	1.6	24.2
L. H.	9.2	1.6	1.2	12.0
L. E.	11.1	2.2	0.2	13.5
R. B.	2.4	2.6	—	5.0
F. S.	29.2	5.0	—	34.2
L. P.	13.1	3.2	—	16.3
J. A.	9.5	5.2	—	14.7
H. K.	8.0	6.0	—	14.0
R. K.	9.1	3.7	—	12.8

anemia. There was no significant increase in urinary radioactivity, and the total excretion remained very low (table 4).

These data motivated the modification of the urinary excretion test to include an extra 24 hour period for urine collection.

The simultaneous administration of a potent intrinsic factor preparation, plus radioactive vitamin B_{12}, to patients with addisonian pernicious anemia resulted in an increase in the urinary excretion of radioactive vitamin B_{12}. In 26 of 33 patients so tested the percentage excreted was increased to within the normal range. Of the remaining seven patients, five showed increases above the range of patients with pernicious anemia, yet below the normal values. Only two continued to have very low excretions despite the administration of intrinsic factor (table 2 and figure 2). The response in these is similar to that described in patients with sprue.[8]

TABLE 4

Effect of Repeated Flushing Injections
Addisonian Pernicious Anemia

	Urine Radioactivity %					
Pt.	Day 1	Day 2	Total	Pt.	Day 1	Day 2	Total
E. B.	0.07	0.30	0.37	T. K.	0.03	0.02	0.05
F. G.	0.53	0.00	0.53	G. S.	0.5	0.1	0.6
J. S.	1.00	0.00	1.0	A. R.	0.3	1.0	1.3
M. J.	0.61	0.50	1.0	F. C.	0.5	0.1	0.6
L. S.	1.32	0.28	1.60	F. P.	0.2	0.3	0.5
S. G.	0.71	0.59	1.3	M. S.	0.0	0.3	0.3
S. R.	0.78	0.17	0.95	S. R.	0.3	0.07	0.37
N. L.	0.5	0.0	0.5	J. T.	0.9	0.5	1.4
D. G.	0.5	0.02	0.52	D. C.	2.3	0.7	3.0
S. W.	1.7	0.97	2.67	B. G.	0.1	0.0	0.1
A. C.	0.4	0.0	0.4	R. F.	0.4	0.0	0.4
R. F.	0.4	0.0	0.4				

Examples of the Application of the Urinary Excretion Test

The practitioner is faced with the necessity of confirming the diagnosis of addisonian pernicious anemia under several circumstances: when presented with a patient who gives a history of having been treated for pernicious anemia and the hematologic data of relapse are unavailable; when the promiscuous use of a variety of hematinics, including vitamin B_{12} or folic acid, has so altered the blood count as to make a diagnosis difficult; to establish the necessity for lifelong vitamin B_{12} treatment in a patient with a megaloblastic anemia in whom the diagnosis of addisonian pernicious anemia is uncertain; and, finally, in patients with the neurologic manifesta-

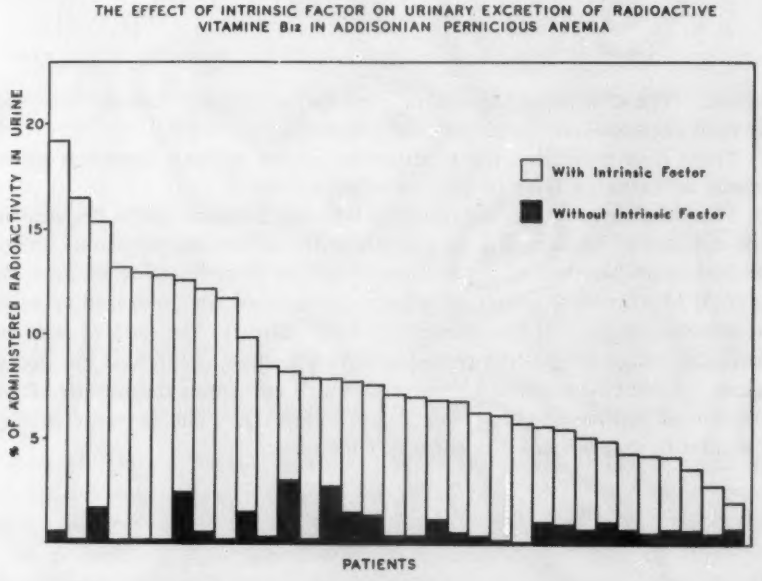


Fig. 2.

tions of combined system disease, without anemia, where pernicious anemia may be the cause.

For the clarification of these problems the urinary excretion test has proved its value in our recent experience on numerous occasions.

Case Reports

Case 1. A 72 year old female had been treated in the pernicious anemia clinic for six years with monthly injections of vitamin B_{12}. She was originally referred to our clinic presumably in hematologic remission. Without the use of intrinsic factor, 12.8% of the orally administered vitamin B_{12} Co^{60} was excreted during the urinary

excretion test. This result was incompatible with a diagnosis of pernicious anemia, and vitamin B_{12} therapy was discontinued.

Case 2. A 54 year old female entered the hospital with a history of prolonged excessive alcoholic ingestion, and treatment during the two weeks prior to admission with multivitamins, including parenteral vitamin B_{12} and liver extract. She had the signs of a peripheral neuritis, a mild macrocytic anemia and gastric achlorhydria after histamine stimulation. The urinary excretion test ruled out the possibility of pernicious anemia, since she excreted 17.4% of the orally administered dose of vitamin B_{12} Co^{60} (before the addition of intrinsic factor).

Case 3. A 34 year old female with psoriatic arthritis had been treated with gold salts. She developed a leukopenia and anemia, and was admitted to the hospital for BAL therapy and blood transfusion. The bone marrow was found to be megaloblastic. On vitamin B_{12} therapy she made an uneventful recovery. The possibility that gold salts and/or BAL produced the megaloblastosis was considered. Three years after recovery, during which time she received vitamin B_{12} parenterally because she insisted it made her feel better, a urinary excretion test confirmed the diagnosis of addisonian pernicious anemia.

Cases 4 and 5. Two patients on the neurology service with findings compatible with the spinal cord manifestations of addisonian pernicious anemia were referred to hematology for evaluation. Neither had an anemia, but both had resistant gastric achlorhydria. The urinary excretion test was normal in both patients, which eliminated addisonian pernicious anemia as the underlying etiology for the neurologic abnormalities.

Case 6. A 44 year old female was referred to the hematology clinic because of fatigue, paresthesias of the hands and feet, cheilosis and a mild anemia. Two years previously she had been treated at another hospital for an anemia. At that time she was transfused with five pints of blood.

On physical examination no abnormalities were noted. The hemoglobin concentration was 10.5 gm.%. The peripheral smear was remarkable for the finding of many macrocytic red blood cells and hypersegmented polymorphonuclear leukocytes. On the basis of these findings a diagnosis of early pernicious anemia was entertained. This was confirmed by the urinary excretion test. Only 3% of the orally administered radioactive vitamin B_{12} Co^{60} was excreted in the urine. When an active source of intrinsic factor was administered concomitant with the vitamin B_{12} Co^{60}, the urinary radioactivity was increased to 8.2%.

Discussion

From the data presented it is apparent that the urinary excretion test can be applied to distinguish between the control patients and those with addisonian pernicious anemia. The differentiation of the patients studied is based upon the percentage of radioactivity excreted in the urine following an orally administered dose of vitamin B_{12} Co^{60}. No overlap was noted in the results of the tests in the two groups, which allows for a clear-cut diagnosis in each individual patient.

Several observers have demonstrated that patients with addisonian pernicious anemia excrete in their stool a greater per cent of orally administered radioactive cobalt-labeled B_{12} than do normal controls. Furthermore, this difference was corrected when the patients with pernicious anemia were given a potent source of intrinsic factor.[9, 10, 11] These observations

indirectly supported the contention of Castle that intrinsic factor is concerned with the absorption of the extrinsic factor, vitamin B_{12}, in the upper gastrointestinal tract.[12, 13] He feels that intrinsic factor acts directly on the intestinal mucosa as a catalyst to some enzymatic process in the epithelium of the upper small intestinal wall.

The results of the urinary excretion test are probably a reflection of the quantity of endogenous intrinsic factor activity, i.e., in addisonian pernicious anemia the low urinary excretion of radioactivity indicates decreased absorption of vitamin B_{12} Co^{60} caused by absent or diminished intrinsic factor activity. In patients with megaloblastic anemia other than addisonian pernicious anemia, such as nutritional folic acid deficiency or nutritional vitamin B_{12} deficiency, where the mechanism is not pathogenetically related to a lack of intrinsic factor, the urinary excretion test is normal. In sprue the urinary excretion of vitamin B_{12} Co^{60} is low in spite of the adequate intrinsic factor, endogenous or exogenous, probably because of a more generalized intestinal absorption defect of another type.

Conclusions

1. A method has been presented for utilizing the urinary excretion of radioactive vitamin B_{12} in the diagnosis of addisonian pernicious anemia.
2. The importance of second- and sometimes third-day flushing doses of parenteral non-radioactive vitamin B_{12} to obtain maximal excretion has been demonstrated.

Summario in Interlingua

Le diagnose de perniciose anemia addisonian in remission es a vices extrememente difficile si observationes del situation hematologic ante le tractamento non es disponibile. Isto es debite al facto que in remission il non ha le classic syndrome de erythropoiese megaloblastic, anemia macrocytic, e leukopenia, sin o con le manifestationes neurologic de morbo de systema combinate.

Le defecto basic in perniciose anemia addisonian es carentia de factor intrinsec, un enzyma gastric essential pro le absorption optimal de vitamina B_{12} oral in le vias gastro-intestinal superior. In remission le diagnose depende del demonstration que le activitate de endogene factor intrinsec es absente.

Un modification del test de excretion urinari (originalmente describite per Schilling) esseva empleate pro essayar le factor intrinsec. Patientes con demonstrate perniciose anemia addisonian e etiam individuos sin ille morbo esseva includite in le studio. Specimens del urina total de 24 horas esseva investigate diurnemente in re lor radio-activitate. Le urina colligite le prime die serviva de controlo. Le secunde die le subjecto a testar recipeva 2 μg de vitamina B_{12} a Co^{60} administrate per via oral ante le prime repasto del die. Simultaneemente ille recipeva un injection intramuscular que contineva 1000 μg de vitamina B_{12} non-radio-active como "dose de chassa."

Le tertie die un secunde injection de 1000 μg de vitamina B_{12} esseva administrate intramuscularmente como "chassa de securitate." Le ultime duo dies del test esseva utilisate como indice del capacitate de excretion maximal de vitamina B_{12} radioactive in omne le subjectos individual. Pro iste ration, il esseva administrate—a parte le vitamina B_{12} radioactive e le dose de chassa del B_{12} non-radio-active—un dose oral de un preparato de factor intrinsec de potentia cognoscite. Isto esseva sequite le

ultime die per un injection intramuscular de 1000 μg de vitamina B_{12} non-radio-active.

Nos describe le resultatos obtenite in 36 patientes de perniciose anemia addisonian e in 24 subjectos de controlo. In le gruppo del patientes con perniciose anemia addisonian le excretion median esseva uniformemente minus que 3 pro cento del total administration oral de vitamina B_{12} radio-active. Le valor median pro le gruppo integre esseva 0,85 pro cento con limites minimo-maximal de 0,05 e 3,0 pro cento. Le 24 subjectos normal habeva un excretion median de 13,3 pro cento con limites minimo-maximal de 5,0 e 34,2 pro cento. Il es a notar que le duo gruppos non habeva un area commun. Nos conclude que le test de excretion urinari in le forma supradescribite pote esser usate in le diagnose de perniciose anemia addisonian in remission. Le secunde dose de chassa de non-radio-active vitamina B_{12} parenteral es importante pro le obtention de un excretion maximal.

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THE RELATIONSHIP BETWEEN HYPERTENSION AND CORONARY OCCLUSION *

By Franz Goldstein, M.D.,† William K. Jenson, M.D., Jerome M. Waldron, M.D., and Garfield G. Duncan, M.D., F.A.C.P.,
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After many decades of intensive experimental and clinical research in hypertension all over the world, there is still no agreement as to the causes and effects of hypertension or as to the indications for treatment. In fact, there is not even agreement as to what constitutes hypertension. Part of the confusion about the various clinical aspects of hypertension undoubtedly stems from the different criteria used in defining hypertension. Among the numerous criteria used, two sets of blood pressures appear to be of most importance. The criteria used by most insurance companies, namely, 140/90 mm. of Hg for the upper limits of normal blood pressure, irrespective of age and sex, have been termed by Fishberg [1] the limits of "ideal" rather than normal blood pressure, because individuals with pressures below these limits are least likely to develop cardiovascular disease in the future. However, many persons with blood pressures in excess of 140/90 mm. of Hg are perfectly healthy and may go through life without cardiovascular disease. Master and associates [4, 5] have sampled the blood pressure readings of 74,000 working men and women between the ages 16 and 65 and have used a purely statistical approach in their evaluation. They divided the subjects into groups according to age and sex, and obtained the means of the systolic and diastolic blood pressures for each group. They considered as definitely hypertensive only those pressures which fell into the range of about two standard deviations (S.D.) above the mean. Pressures within one S.D. of the mean were considered normotensive and those between one and two S.D. were borderline hypertensive according to this classification. While such a classification is not necessarily biologically correct, it offers certain advantages. Since by the nature of these criteria about 5% ‡ of the population will fall into the hypertensive range, it is easy to relate any given factor in a population to the incidence of hypertension.

Until recently it had been generally accepted that hypertension is an important predisposing factor in the pathogenesis of coronary occlusion.[2] Master and his associates in 1939 [3] agreed with previous workers on this point, and found in their own series of 500 patients that 56% of 387 men

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‡ Actually, ± 1.96 S.D. includes 95% of individuals, leaving 2.5% on either extreme, but Master extended the group to include 5% of the population with highest blood pressures.

and 80% of 113 women with coronary occlusion had antecedent hypertension.

More recently Master reversed his opinion and, on the basis of his newly adopted criteria, came to the conclusion that "hypertension, if it is a factor at all, is not the all important one in men who sustain coronary occlusion," but that "hypertension was a very significant factor in women who sustain coronary occlusion." These conclusions were based chiefly on the finding that more than 70% of 500 men who sustained coronary occlusion were normotensive prior to that event. Among the 100 women with coronary occlusion, 71% were hypertensive and only 29% were normotensive.[6]

Sigler,[11] in a recent analysis of 1,160 patients and utilizing criteria which may be fitted into Master's classification, came to similar conclusions. On the basis of the finding that more men with coronary occlusion were normotensive than hypertensive, and on the basis of certain discrepancies between

TABLE 1

The Incidence of Hypertension among 200 Patients with Myocardial Infarctions. Consecutive Unselected Patients Gathered from the Autopsy Files of the Pennsylvania Hospital

	Males			Females		
	Total No. Patients	No. with Hypertension	Per Cent with Hypertension	Total No. Patients	No. with Hypertension	Per Cent with Hypertension
20–29 yrs.	0	0	0	0	0	0
30–39 yrs.	8	1	12.5	2	2	100.0
40–49 yrs.	16	7	43.7	7	4	57.2
50–59 yrs.	32	9	28.1	9	2	22.2
60–69 yrs.	40	10	25.0	18	9	50.0
70– yrs.	39	10	25.7	29	5	17.2
Totals	135	37	27.4	65	22	33.9

the age incidences of hypertension and coronary occlusion, Sigler concluded that hypertension is not causally related to coronary occlusion in either sex.

The question whether hypertension is causally related to coronary occlusion and myocardial infarction, as well as to a number of other cardiovascular complications, is a crucial question, since on its answer depends to a large extent the clinician's decision as to treatment. It occurred to us that the data presented by Master [6] and by Sigler [11] lend themselves to a different and perhaps more nearly correct interpretation, and such will be presented in this article, with some additional data gathered at the Pennsylvania Hospital.

MATERIAL AND METHODS

In this analysis we have used the data presented by Master [6] and Sigler,[11] and our own. The autopsy records of the Pennsylvania Hospital for the years 1947–1954 were reviewed, and the last consecutive 200 cases since

TABLE 2

The Incidence of Hypertension among 1,160 Patients with Coronary Occlusion (Modified According to Data Published by Sigler*)

	Males			Females		
	Total No. of Patients	Number with Hypertension	Per Cent with Hypertension	Total No. of Patients	Number with Hypertension	Per Cent with Hypertension
20–29 yrs.	5	0	0	0	0	0
30–39 yrs.	60	9	15.0	6	3	42.9
40–49 yrs.	271	49	18.1	28	10	35.7
50–59 yrs.	379	80	21.1	79	50	63.3
60–69 yrs.	190	51	26.8	82	50	61.0
70–79 yrs.	41	12	29.2	18	10	55.6
Totals	946	201	21.2	214	123	57.5

* Ann. Int. Med. 42: 369, 1955.

1947 with myocardial infarction on postmortem examination were analyzed. The highest repeated and sustained blood pressure was recorded in each instance. When only post-infarction blood pressures in the normotensive or hypotensive range were available, the patients were considered normotensive, even though in some instances there was suggestive evidence of previous hypertension. The patients were grouped according to sex and age by decades. The blood pressures were classified according to Master's criteria into normotensive and hypertensive pressures. Patients with borderline hypertensive pressures were included with the normotensive patients. We have included patients over the age of 65, and have used Master's criteria of hypertension of the oldest available group (60 to 64 years) in these patients. Sigler's figures also extend beyond the age of 65. The error which might be introduced in these older age groups is believed to be insignificant in the group of patients 65 to 69 years old. The figures in the oldest age groups (70 and up) would have to be viewed with less confidence and will not be subjected to detailed analysis.

TABLE 3

The Incidence of Hypertension among 600 Patients with Coronary Occlusion (Modified According to Figures Published by Master*)

	Males			Females		
	Total No. of Patients	Number with Hypertension	Per Cent with Hypertension	Total No. of Patients	Number with Hypertension	Per Cent with Hypertension
25–39 yrs.	27	6	22.2	—	—	—
40–49 yrs.	167	43	25.7	22	14	63.7 (35–49 yrs.)
50–59 yrs.	243	68	28.0	46	32	69.6
60–64 yrs.	63	19	30.4	32	25	78.2
Totals	500	136	27.2	100	71	71.0

* Circulation 8: 170, 1953.

Sigler divided his patients into four blood pressure groups. His group I (up to 140/90 mm.) of Hg is definitely normotensive by almost all classifications. Group II (141–160/91–100 mm. of Hg) roughly represents the borderline group of Master's classification. All of Sigler's group IV patients (over 200/110 mm. of Hg) and most of his group III patients

TABLE 4

Incidence of Hypertension among 1,960 Collected Patients with Coronary Occlusion

		Males			Females		
		Total No. Patients	No. with Hypertension	Per Cent with Hypertension	Total No. Patients	No. with Hypertension	Per Cent with Hypertension
20–29 yrs.	M.	—	—	—	—	—	—
	S.	5	0	0	—	—	—
	P.H.	—	—	—	—	—	—
	Totals	5	0	0	—	—	—
(25–39) 30–39 yrs.	M.	27	6	22.2	—	—	—
	S.	60	9	15.0	7	3	42.9
	P.H.	8	1	12.5	2	2	100.0
	Totals	95	16	16.8	9	5	55.5
40–49	M.	167	43	25.7	(35–49 y.) 22	14	63.7
	S.	271	49	18.1	28	10	35.7
	P.H.	16	7	43.7	7	4	57.1
	Totals	454	99	21.8	57	28	49.1
50–59	M.	243	68	28.0	46	32	69.6
	S.	379	80	21.1	79	50	63.3
	P.H.	32	9	28.1	9	2	22.2
	Totals	654	157	24.0	134	84	62.7
60–69	M.	63	19	30.4	32	25	78.2
	S.	190	51	26.8	82	50	61.0
	P.H.	40	10	25.0	18	9	50.0
	Totals	293	80	27.3	132	84	63.6
70–	M.	—	—	—	—	—	—
	S.	41	12	29.2	18	10	55.6
	P.H.	39	10	25.6	29	5	17.4
	Totals	80	22	27.5	47	15	31.9
Grand totals		1581	374	23.7%	379	216	57.0%

Abbreviations:
M. Master's data.
S. Sigler's data.
P.H. Pennsylvania Hospital data.
Further explanations given in text.

(161–200/101–110 mm. of Hg) would fall into Master's hypertensive range. In the present analysis Sigler's groups III and IV were therefore lumped together as the hypertensive group (table 2). In table 2 are shown Sigler's data abbreviated to indicate the numbers and percentages of patients with coronary occlusion and hypertension arranged by sex and decades as com-

pared with the total numbers (100%) of patients who had sustained coronary occlusion.

Master's data have been similarly grouped in the present analysis, i.e., the patients of each sex were grouped by decades and the numbers and percentages of patients with hypertension in each group were compared with the total numbers of patients with coronary occlusions (table 3).

In table 4 the data of all three series are for convenience added together and the combined totals and percentages are given.

It will be seen that there is fairly good agreement between the percentages obtained in the three series of patients, especially in the age groups including sufficiently large numbers of patients to be of significance. By adding together the patients of all three series we have increased the numbers in all groups thus adding significance particularly to the groups with smaller numbers. The data collected in this series constitute, to the best of our knowledge, all patients reported in the United States literature with coronary occlusion and blood pressures analyzed according to the newer criteria of Master.

Such differences between the percentages in the three series as do exist may be explained primarily by the relatively small numbers of patients in some groups. The differences are relatively small in the groups with larger numbers of patients. They may in part be explained by the somewhat different approach used in the studies. Master's figures are based on consecutive patients seen in private practice. The age of the coronary occlusion or the number of occlusions in patients with several occlusions was not considered. The diagnostic criteria used were presumably the commonly accepted clinical and electrocardiographic criteria. Sigler's patients were also patients seen in clinical practice with a clinical diagnosis of coronary occlusion. His patients were selected to the extent that the group included only patients with previous blood pressure records, and they were all patients with their first coronary occlusion.[10, 11] Our patients were unselected autopsied hospital cases in whom the diagnosis of myocardial infarction was made histologically by a pathologist. In most instances the infarction was fairly recent, but in some patients it was old, i.e., it had occurred at a considerably younger age than the age of death which was recorded. When we consider these different avenues of approach, each with its shortcomings, and the somewhat overlapping blood pressures in Sigler's series, it is surprising how closely the results agree.

Results

Of the total 1,960 surveyed cases of coronary occlusion, 1,581 occurred in males and 379 in females, a ratio of 4.2:1. Of the 1,581 males with coronary occlusion, 374 (or 23.7%) had hypertension as defined by Master's criteria. Of the 379 women, 216 (or 57.0%) had associated hypertension.

The ratio of males to females with coronary occlusion associated with hypertension was 1.73 : 1.

In males, coronary occlusions were rare in the third decade; their incidence increased rapidly in successive decades, and reached a maximum in the sixth decade, followed by a marked drop in the seventh decade (particularly significant in Sigler's series, not apparent in our series and not determinable in Master's series extending only to the age of 64). In females, no coronary occlusions were observed in the third decade and relatively few were recorded in the following two decades. The incidence then rose markedly and reached a maximum in the seventh decade in Sigler's and the Pennsylvania Hospital series, and might also have been present in Master's series if this had been extended beyond the age of 65. However, the difference in incidence between the sixth and seventh decades is not very remarkable. This is in marked contrast to the males, where a reduction of almost 50% in the incidence of coronary occlusion occurred after the age of 60.

Hypertension among males was not seen in any of the five patients who suffered a coronary occlusion before the age of 30. In the next decade 16.8% of the males with coronary occlusion had hypertension, and in the subsequent decades the corresponding figures were 21.8, 24.0, 27.3 and 27.5%. Thus among males 40 years and older the percentage of coronary occlusions associated with hypertension remains fairly constant from decade to decade. Among the females, five out of nine (55.5%) of the subjects in their fourth decade with coronary occlusions had hypertension, and in subsequent decades the percentages of hypertensive women with coronary occlusions were 49.1, 62.7, 63.6 and 31.9%. Again, it is seen that among females between 30 and 70 the percentages of patients in whom coronary occlusion was associated with hypertension did not differ greatly from decade to decade. When the absolute numbers of hypertensive patients with coronary occlusions in the two sexes were compared, it was found that with increasing age (until 70) the male preponderance became progressively less marked, until in the seventh decade the number of coronary occlusions associated with hypertension was practically identical in both sexes.

Interpretation and Discussion

The majority of men with coronary occlusion and a sizable minority of women with coronary occlusion have blood pressures which are normal or borderline normal by Master's criteria. However, when Master's criteria of hypertension are used, precisely 5% of individuals may be expected to have hypertension in any group large enough to provide an adequate sample, provided no biasing selection is carried out and provided Master's own series represents a fair sample of the U. S. population. Since all data in this survey came either from New York City itself, where Master conducted his survey,

or from Philadelphia, possible differences between big city and rural populations would not interfere with the validity of the data and conclusions.

Therefore, it is our interpretation that if 23.7% of males with coronary occlusion and 55.0% of females with coronary occlusion had hypertension of a degree which is encountered in only 5% of the population, it follows that hypertension occurs 4.75 times more frequently in this group of males and 11.5 times more frequently in the females with coronary occlusion than in otherwise comparable individuals without coronary occlusion. The fact that the majority of males with coronary occlusion have normal blood pressures by the criteria of Master does not warrant the conclusion that coronary occlusion is not related to hypertension. On the contrary, the higher incidence of hypertension among both males and females with coronary occlusion as compared with the incidence of hypertension in the general population warrants the conclusion that there is a definite correlation or association between hypertension and coronary occlusion.

The figures cited here indicate the incidence of hypertension among patients with coronary occlusion. They do not give quantitative information on the incidence of coronary occlusion among hypertensive individuals, compared with the incidence of coronary occlusion among normotensive individuals. Such information would be more valuable because it would permit the estimation of the probability of the occurrence of coronary occlusion among normotensive and hypertensive persons.

If different criteria of hypertension are accepted one obtains somewhat different figures for the incidence of hypertension among patients with coronary occlusion. Master has also provided figures on the incidence of blood pressures falling outside the one S.D. limits (i.e., approximately 16.7% in either direction from the mean) among patients with coronary occlusions. If one chooses to accept one S.D. from the mean as the criterion of hypertension, one finds that a male with a coronary occlusion is about twice as likely to have this degree of hypertension as is a male of similar age without coronary occlusion. Applying the same criteria to females, one finds that hypertension of this degree is found 4.75 times more frequently among females with coronary occlusion than among females without this disease. These incidence figures are not to be taken too literally, since they are based on arbitrary blood pressure limits, but they do point very definitely to a correlation between hypertension and coronary occlusion.

As further evidence against a causal relationship between hypertension and coronary occlusion, Sigler [11] states: "That the incidence of both conditions [hypertension and coronary occlusion] increases with advancing age is well established. If hypertension should be an important underlying cause of coronary occlusion, we would expect the increase of coronary occlusion to correspond closely to the increase in hypertension as age progresses. Furthermore, if there is a causal relationship it is hard to understand why the incidence of hypertension is so much greater in the female

group of coronary occlusion, at the same time that the incidence of coronary occlusion is so much greater in the males and in cases with low blood pressure levels."

Our interpretation based on the data in this report and consistent with current concepts on atherosclerosis is as follows. In males the increase in the number of coronary occlusions extends through the sixth decade. The subsequent drop may be explained by the earlier age of death among males and the fact that fewer males are available in the seventh decade to die of any cause. Also, it is conceivable that many of the males susceptible specifically to hypertension and coronary artery disease have already succumbed to their disease before they reach the seventh decade. As Sigler has shown in another extensive analysis,[10] only 50.9% of males with coronary artery disease as manifested by angina and/or coronary occlusion lived beyond the age of 60 (vs. 59.2% females). In females the incidence of coronary occlusions climbs through the seventh decade, although the rise from the sixth to the seventh decades is minimal and probably not significant. Again, it may be countered that females generally live longer, and relatively more women are available in the seventh decade who are susceptible to the damaging effects of hypertension and atherosclerosis and who will develop coronary occlusions.

It was pointed out that the percentages of patients with hypertension and coronary occlusion for each sex in the age groups including large enough numbers to be significant are fairly similar (males: 21.8, 24.0, 27.3; females: 49.1, 62.7, 63.6). This could indicate that hypertension as a factor in the pathogenesis of coronary occlusion is of a different relative but fairly constant significance in each sex. It is relatively more important in the female, indicating perhaps the absence of another atherogenesis-promoting factor (or factors) or the presence of protective factors in the female. On the other hand, the presence and influence of other atherogenic factors in the male (differences in lipid metabolism, hormonal differences[7, 9, 12]) would account for the higher incidence of coronary occlusion in the male and hence the relatively less important rôle which hypertension plays in that sex with respect to causing coronary occlusions. This point is further borne out by the observation that in both sexes the absolute numbers of coronary occlusions associated with hypertension tend to approach each other with increasing age until in the seventh decade the numbers are practically identical. Younger women are less prone to develop atherosclerosis and coronary occlusion with or without hypertension, and this may well be due to the protection afforded premenopausal women by their high estrogen production. Castrated women do not manifest this protection.[13] It is reasonable to assume that if hypertension is a factor in accelerating atherosclerosis, it would require years before the effects of hypertension in even a susceptible individual might become manifest. Hence the finding that hypertension appears to influence the incidence of coronary occlusion mostly

in the relatively older age groups is a logical one to expect. Conversely, hypertension of extreme severity but short duration (malignant hypertension) results in the death of most patients by renal failure or cerebrovascular hemorrhage before significant changes in the coronary arteries can occur. It is such a group of patients [8] that was quoted by Sigler in support of his thesis that hypertension is not related to coronary atherosclerosis and coronary occlusion.

The present analysis does not take into account the importance of diabetes mellitus in accelerating atherosclerosis and causing coronary occlusions. In passing, it may be noted that in analogy to hypertension, and possibly for similar reasons, diabetes mellitus is much more frequently associated with coronary occlusions in females than in males.[2]

In summary, it is postulated that hypertension in both sexes is *one* of several factors involved in atherogenesis, atherosclerosis and the causation of coronary occlusion and myocardial infarction. Other factors in these processes presumably are diabetes mellitus, certain disturbances in lipid metabolism, and the sex hormones. Up to the menopause, women enjoy a fair degree of protection from atherosclerosis and from the accelerating effects of hypertension on atherogenesis. After menopause the number of coronary occlusions associated with, and presumably causally related to, hypertension approaches and eventually equals the number observed in men of similar age. Therefore, the hypertensive factor is presumed to be of equal absolute importance in both sexes. Because other factors operate additionally in the male to accelerate atherogenesis and to cause coronary occlusions, hypertension is of relatively less importance in the male.

The positive correlation between hypertension and the incidence of coronary occlusion should be considered, among other factors, in deciding whether a patient with hypertension should receive hypotensive therapy.

SUMMARIO IN INTERLINGUA

Le previemente acceptate relation causal inter hypertension e occlusion coronari ha recentemente essite attaccate per duo investigatores de reputation qui applicava al analyse de lor datos le plus recente criterios de hypertension secundo le proponimentos de Master. Le argumentos principal contra un relation causal inter hypertension e occlusion coronari esseva le observationes (1) que le majoritate del masculos con occlusion coronari ha pressiones sanguinee intra le limites normal e (2) que il existe un discrepantia inter le distribution per etate in hypertension e occlusion coronari. In le presente articulo le datos del justo-mentionate investigatores es re-examinate. Nove datos es addite que esseva obtenite ab le Hospital Pennsylvania. Le numero total del casos de occlusion coronari includite in nostre studio es 1960. Inter le 1581 masculos con occlusion coronari, 374 (o 23, 7 pro cento) habeva hypertension secundo le criterios de Master. Inter le 379 femininas, 216 (o 57, 0 pro cento) habeva hypertension associate. Proque hypertension secundo le definition de Master occurre in exactemente 5 pro cento del population general e proque in le segmento del population que nos seligeva a causa del presentia de occlusion coronari le occurrentia de hypertension esseva 23, 7 pro cento in masculos e 57, 0 pro cento in femininas, nos conclude

que hypertension es significativemente plus frequente in e masculos e femininas con occlusion coronari que in le resto del population. Le retardate frequentia maximal de occlusion coronari in femininas es explicate per le protection que plus juvene feminas obtene ab lor estrogenos. Le numeros absolute de occlusion coronari associate con hypertension tende a equalisar se in le duo sexos durante le decennios plus avantiate del vita. Ergo, hypertension como co-factor causal in le pathogenese de occlusion coronari possede apparentemente un simile signification absolute in ambe sexos, sed relativemente illo es minus importante in masculos a causa de altere factores—per exemplo certe disturbationes del metabolismo lipide e influentias hormonal —que age additionalmente o plus extensemente in le masculo.

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RESERPINE–HYDRALAZINE COMBINATION THERAPY OF HYPERTENSIVE DISEASE, WITH HYDRALAZINE IN DOSES GENERALLY BELOW THE "TOXIC RANGE" * †

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Although mild and labile hypertension frequently responds to Rauwolfia and its derivatives,[1, 2, 3] more advanced hypertensive disease usually requires an additional pharmacologic agent.[4, 5, 6, 7, 8] Hydralazine has proved a useful supplementary drug in many such cases. At the dosage levels employed, however, "toxic" side effects have appeared in many instances.[9, 10] As many as 12% or more of patients receiving over 300 mg. of hydralazine daily may develop arthralgia and/or a "lupus-like" syndrome.[10] Other instances of toxicity reported in the literature and presented in summary form in table 1 suggest that high dosage level may be an important factor in the genesis of undesirable reactions. If satisfactory therapeutic results could be achieved with lower dosage, the range of usefulness of hydralazine might be widely extended. To investigate this possibility, the following study was carried out on hypertensive patients with hydralazine restricted to 300 mg. or less daily. The drug was administered with reserpine, since it may be effective in smaller doses when so combined. For comparison, a second group of patients was given reserpine alone, in an amount generally comparable to that given on the combination regimen.

Material and Methods

The test subjects were 25 patients who had had sustained hypertension above 150/100 mm. of Hg, known for an average period of three and one-half years. Many had previously shown no response to such regimens as the rice diet, sodium restriction and/or sedation with barbiturates. Seventeen had grade I fundal vascular changes, seven grade II, and one grade III. With the exception of three patients who had slight cardiomegaly, the hearts and lungs were roentgenographically normal. Electrocardiograms showed no abnormalities considered to be clinically significant. Blood urea nitrogen was below 20 mg.%, and routine urinalysis and complete blood counts were within the normal range.

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TABLE 1

Author and Article	Dose of Hydralazine/q.d.	Duration of Rx.	Side Reactions	Frequency of Reactions at Doses
Muller, J. C., Rast, C. L., Pryor, W. W., and Orgain, E. S.: Late systemic complications of hydralazine (Apresoline) therapy, J. A. M. A. **157**: 894 (Mar. 12) 1955	300–600 mg. (average, 446)	6–12 mos. (average 10.3)	"Collagen-like reaction" similar to LE in one case. "Collagen-like reaction" similar to rheumatoid arthritis in six cases. Aching and stiffness of joints, fever, sore throat, pleuritis, malaise, etc. LE cells were found in 2 cases	13% (7/53)
Morrow, J. D., Schroeder, H. A., and Perry, H., Jr.: Studies on the control of hypertension by Hyphex. II. Toxic reactions and side effects, Circulation **8**: 829 (Dec.) 1953	600–900 mg.	4–23 mos.	Arthritis and collagen-like disease	6.2% (16/258)
		2 days–3 weeks	Fever	2.3% (6/258)
Kaufman, M.: Pancytopenia following use of hydralazine (Apresoline), J. A. M. A. **151**: 1488 (Apr. 25) 1953	400 mg.	7 mos.	Pancytopenia (in peripheral blood, not in bone marrow)	Case report
Moser, M., Syner, J., Malitz, S., and Mattingly, T. W.: Acute psychosis as a complication of hydralazine therapy in essential hypertension, J. A. M. A. **152**: 1329 (Aug. 1) 1953	500 mg.	12 days	Acute psychotic episode—manic type behavior. (Cleared 24 hours after drug was stopped)	Case report
Mandelbaum, H., Brook, J., and Mandelbaum, R. A.: Bleeding peptic ulcer complicating hydralazine and hexamethonium bromide therapy, J. A. M. A. **155**: 833 (June 26) 1954	100 mg.	3 days	Melena (activation of peptic ulcer). On hexamethonium, 25 mg. i.m. q 4 h too. (No good relationship or proof that Apresoline caused melena)	Case report
Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. A.: Rheumatic and febrile syndrome during prolonged hydralazine treatment, J. A. M. A. **154**: 23 (Jan. 2) 1954	400–800 mg. (average, 640)	6–22 mos. (average 12)	(1) mild rheumatoid form and (2) severe febrile form resembling lupus E. 8 patients had (1) mild rheumatoid form and 5 patients had (2) severe febrile form resembling lupus E. 2/5 had LE cells	9.4% (13/139)

TABLE 1—(*Continued*)

Author and Article	Dose of Hydralazine/q.d.	Duration of Rx.	Side Reactions	Frequency of Reactions at Doses
Perry, H. M., Jr., and Schroeder, H.: Syndrome simulating collagen disease caused by hydralazine (Apresoline), J. A. M. A. **154**: 670 (Feb. 20) 1954	250–750 mg. (average, 460) 3 had 250 1 had 300 Rest were over 300	2–22 mos. (average 12)	Arthralgia. Symptoms similar to rheumatoid arthritis, symptoms similar to LE. 1 patient had LE cells	8.1% (17/211)
Slonim, N. B.: Arthralgia, headache, prostration and fever during hydralazine therapy, J. A. M. A. **154**: 1419 (Apr. 24) 1954	600 mg.	10 mos.	Arthralgia, headache, prostration and fever	Case report
Manter, W. B.: Late reaction to hydralazine (Apresoline) therapy, New England J. Med. **250**: 835 (May 13) 1954	600 mg.	9 mos.	Malaise, fever, arthralgia, weight loss, etc. Positive LE cells	Case report
Reinhardt, D. J., and Waldron, J. M.: Lupus erythematosus-like syndrome complicating hydralazine (Apresoline) therapy, J. A. M. A. **155**: 1491 (Aug. 21) 1954	600 mg.	8 mos.	LE syndrome. Biopsy of rheumatic nodule showed collagen necrosis	Case report
Shackman, N. H., Swiller, A. I., and Morrison, M.: Syndrome simulating acute disseminated lupus erythematosus: appearance after hydralazine therapy, J. A. M. A. **155**: 1492 (Aug. 21) 1954	300 mg. for 3 mos.; 200 mg. for rest of time	9 mos.	LE syndrome. Positive LE cells. False-positive STS	Case report

The patients were divided into two groups. Group I received reserpine alone, Group II the reserpine-hydralazine combination. Each patient had a 12 week course of test medication and a similar period of placebo therapy, separated by a three week interval during which neither placebo nor test drugs were given. Thus, a typical subject would have placebo for 12 weeks, nothing for three weeks, then test medication for 12 weeks. This order was reversed in other patients, so that approximately half of each group receiving the placebo initially had the remainder starting on active medication. The nature of the tablets dispensed in all cases was known neither to physician nor to patient, placebo and test tablets being identical in appearance (the "double-blind" procedure).

In all instances, tablets were taken just prior to meals. During administration of the active medications, Group I patients received reserpine, 0.5 mg. daily in the morning for three weeks, 0.5 mg. morning and evening for the second three weeks (total, 1.0 mg.), and 0.5 mg. three times daily (total, 1.5 mg.) for the final six weeks. Group II patients took 0.1 mg. reserpine and 25.0 mg. hydralazine three times daily for three weeks; 0.2 mg. reserpine and 50.0 mg. hydralazine three times daily for the second three weeks; 0.3 mg. reserpine and 75.0 mg. hydralazine three times daily for the next three weeks; and 0.4 mg. reserpine and 100 mg. hydralazine three times daily for the final three weeks.

Each subject was examined at three week intervals over the entire period of six months. Patients failing to report regularly to the clinic were dropped from the series. Blood pressures from the right arm were recorded immediately after the patient had assumed a reclining position, and again after *each* of two consecutive five-minute intervals of rest. Thus, the patients rested, lying supine, for 10 minutes between the first and last readings. Systolic pressure was recorded as that at which sounds first were heard, and the pressure where all sounds disappeared was taken as the diastolic value.[11]

Data were assembled for analysis as follows: Means for systolic and diastolic pressures were calculated for each visit. In the comparison of blood pressures during placebo and treatment periods, blood pressure averages were determined for the six weeks just prior to the program and for the last half (six weeks) of each study period (placebo and test). Average systolic and diastolic values during the latter half of each interval were then compared.

In addition, data were analyzed statistically, including all subjects of each group in the study, to compare the collected total placebo and test observations. It was felt that this approach would provide significance to the tests beyond that afforded by the comparison of effects in individual patients alone.

Reserpine Results

Blood Pressure: Twelve patients completed treatment periods, while 10 have thus far also finished their placebo period. Of the four individuals

with grade II fundi, one showed a diastolic blood pressure fall of 15 mm. Hg, but the others failed to show diastolic changes. The systolic blood pressure fell 22 mm. Hg in one case, and 26 in another, and stayed constant in the remaining two cases. The eight subjects with grade I fundi had more prominent blood pressure changes. Four of these milder cases showed a systolic drop exceeding 25 mm. Hg, and three showed a diastolic fall greater than 20 mm. Hg. The combined data of all patients completing the regimen of reserpine and placebo are shown in table 2. The systolic blood pressure fell from an initial average of 192 to a final average of 172 after reserpine. The diastolic blood pressure fell from an initial average of 112 to a final average of 97 after reserpine. Thus, the average systolic blood pressure was reduced by 20 mm. Hg and the diastolic blood pressure by 15 mm. Hg with reserpine alone. The P value of the systolic difference was 0.1, indicating that the change could not be considered statistically significant. Possibly a greater number of subjects would have increased the meaning of the difference had the same trend continued. The diastolic

TABLE 2
Average Blood Pressure—All Cases

	Reserpine (12 cases)		Placebo (11 cases)	
	Systolic	Diastolic	Systolic	Diastolic
Initial	192	112	184	105
Final	172	97	192	109
P Value	0.1	0.013	0.58	0.46

fall of 15 mm. Hg, on the other hand, is considered definitely meaningful at the 1% level of probability with a P value of 0.013 (table 2).

In sharp contrast are the data obtained while the subjects were on the placebo period. Here the initial systolic mean was 184, whereas the final average was 192 mm. Hg, representing a rise of 8 mm. Systolic pressure on placebo fell 14 mm. Hg in one case and 20 mm. Hg in another. In the remaining patients, it stayed level or rose slightly. The initial diastolic mean of 105 rose to 109. Only two patients showed any diastolic fall, one of 8 mm. Hg, and a second of 10 mm. Hg. The diastolic blood pressure otherwise remained level or rose slightly. Pressure increases during the placebo period probably result from diminishing therapeutic effect of previously administered reserpine. Six of the 10 cases were given the placebo following the active principles, and blood pressures in four of these rose from the therapeutically reduced levels to their former elevated levels. These pressure increments are not, however, statistically significant (P values greater than 0.1 in both systolic and diastolic).

Associated Phenomena

A regression of fundal vascular abnormalities was not observed during the reserpine study. A lack of retinal vascular change during Rauwolfia-derivative induced blood pressure reduction has been noted previously.[12] The slightly enlarged heart silhouette observed in three cases was similarly not obviously influenced by therapy. No significant bradycardia was encountered. The body weight, however, rose about 2 kg. in four instances, with an average increase of about 1 kg. Nine of the 13 cases given reserpine had initial symptoms of headache, weakness and tension. These symptoms completely disappeared in four cases. These and other individuals volunteered that they "felt better" while on the medication.

The usual side effects of reserpine were frequently encountered and have been documented elsewhere. Six individuals noted mild nasal congestion, but this was troublesome in only one instance. Two patients while receiving reserpine developed prominent arthralgias, primarily of the knees and ankles, that gradually disappeared over a two week interval when the medication was withheld. Five other individuals displayed slight pitting edema of the ankles, and a third had mild menorrhagia.

Studies on Reserpine-Hydralazine Combinations

A total of 13 cases has completed the program on the combination of reserpine plus hydralazine, and the placebo period, with an additional subject finishing a placebo course. Table 3 shows the average blood pressure observations in all subjects, regardless of whether pressure changes occurred during the period of study. While they were on the active agents, mean systolic blood pressure was reduced from 209 mm. Hg to 165 mm. Hg, an average systolic drop in all individuals of 44 mm. Hg. The P value of the systolic difference was less than 0.01. Diastolic pressure mean in the group fell from 118 mm. Hg to 93 mm. Hg, a reduction of 25 mm. Hg.

As with the systolic pressures, the P value of the diastolic change is less than 0.01. The reduction in group mean pressures in each is therefore highly significant. During the period of active therapy, systolic blood pressure reductions greater than 40 mm. Hg occurred in seven subjects, and greater than 25 mm. Hg in 10. The diastolic pressure fell more than 30 mm. Hg in five cases, and more than 20 mm. Hg in nine cases. During the placebo period an average systolic pressure of 195 mm. Hg rose to 205 mm. Hg. The initial diastolic blood pressure of 107 mm. Hg rose 8 mm. Hg to a final value of 115 mm. Hg. As in the reserpine cases, the slight pressure increases are attributed to the diminishing therapeutic effect of previously administered active drugs. In each instance the pressure rose to its former high values. P values indicate that these differences are not statistically significant (table 3).

Four subjects given the drug combination had prominent grade II fundal

vascular changes. Although improvement in these vessels was not observed, in contrast to the findings of Serpasil alone three of these four cases exhibited major blood pressure responses to treatment. One of these three individuals had previously failed to show any blood pressure response to reserpine alone. The remaining nine cases completing treatment had grade I vascular changes in the fundi. Generally speaking, although this did not hold invariably, the individuals with grade I fundi were found to show a greater blood pressure fall than those with fundal changes relatively more advanced in severity.

Associated Phenomena

No improvement occurred in the retinal vessels or in the cardiac enlargement present in one case. In contrast to the slight weight gain of subjects on reserpine, the patients receiving combination therapy showed no definite weight change trends. Certain cases gained 1 to 3 kg. while others remained at constant weight or showed a mild loss. Bradycardia was not

Table 3

Average Blood Pressure—All Cases

	Reserpine and Hydralazine (13 cases)		Placebo (14 cases)	
	Systolic	Diastolic	Systolic	Diastolic
Initial	209	118	195	107
Final	165	93	205	115
P Value	less than 0.01	less than 0.01	0.38	0.19

noted. A complete disappearance of headache occurred in five of seven subjects with this initial complaint. In the majority of instances, although specific symptoms could not be elicited at the start of treatment, the subjects later volunteered a feeling of "relaxation," of being "separated from problems," or of greater calm during the administration of therapy, not encountered while receiving the placebo.

Distressing side effects of the medication were minimal and in no instance required cessation of therapy or alteration of the dosage. One case while receiving the combination therapy developed a minimal arthralgia of the ankles that was not present during placebo administration. Her previous headache disappeared, however, and she considered herself "improved" by the medication. This subject had previously received reserpine alone without any complaint or benefit. Her symptoms, although transient on medication, were therefore perhaps the result of hydralazine. Laboratory findings in this case, including attempts to demonstrate "lupus-cells," were not revealing. While receiving therapy, six patients developed nasal congestion (associated in two instances with slight dependent edema) that was

absent during the placebo period. Drowsiness of a mild degree was noted in two of these cases. No other side effects were noted.

Discussion

The above data, as expressed particularly in table 2, illustrate that reserpine will produce a significant blood pressure fall in approximately 60% of individuals with sustained and prominent hypertensive vascular disease. When it is used with hydralazine in subjects comparable to those given the single agent, more profound and more frequent hypotensive responses have been achieved. The average blood pressure fall and the number of patients with diastolic reductions greater than 25 mm. Hg in our series compare very favorably with the results in other series in which much greater amounts of hydralazine were used.[6, 8] It has been stated that reserpine is the drug of choice for patients whose blood pressure is labile and whose degree of blood pressure elevation is slight to moderate.[13] Our experience, however, indicates that this agent may also be of value even if the hypertension is of considerable degree and has been sustained for as long as five years or more without known remission. In some instances a hypotensive response to Rauwolfia derivatives may be delayed until treatment has been prolonged for several months.[12] For that reason, if an extension of the present program had been possible, it is very likely that the percentage of patients with blood pressure reductions on either therapeutic regimen would have been somewhat greater.

It was of interest that bradycardia, frequently reported as a feature of therapy with Rauwolfia and its derivatives, was not present to a significant degree in our subjects. As with the findings of other workers, however,[12] the improvement in blood pressure could not be associated with definite improvement of the vascular state in the fundi. This may result, partly at least, from the fact that the degree of fundal vascular change in all but one of the patients was relatively mild, that is, not greater than grade II in severity.

The usual side effects of nasal congestion, occasional sleepiness, and in two instances some depression, are in close accord with the findings of others.[3, 5] Of interest, however, were seven cases treated with either reserpine or reserpine and hydralazine who showed dependent edema not clearly associated either with bradycardia or with a blood pressure fall. In women during the premenstrual phase, this edema, of "pitting" nature, occasionally was prominent. Menorrhagia and metrorrhagia seen in one of our subjects on reserpine therapy is in accord with previous observations.[14]

Conclusions

1. Hydralazine in daily doses of 300 mg. or less, when combined with reserpine, produced a significant hypotensive effect in a large majority of our patients with fixed hypertension of over three years' duration.

2. Therapeutic effectiveness was attained without significant toxicity in our series. This is in accord with the impression that the incidence of toxicity is at least partly a function of dosage.

3. If further study substantiates this belief, the range of usefulness of hydralazine may be greatly extended, provided the dosage is kept at moderate levels.

4. Reserpine alone produces a significant hypotensive effect in certain patients with fixed and prominent hypertension. This agent may be tried initially in hypertensive patients, with the subsequent addition of hydralazine in moderate doses as indicated by the therapeutic response.

Summario in Interlingua

Hydralazina, in combination con un o plure altere drogas, se ha provate un bon agente antihypertensive. Nonobstante, casos numerose de toxicitate e specialmente del apparition de un syndrome "lupusoide," ha resultate in le limitation de su uso. Un revista del litteratura suggere le notion que in le casos reportate de toxicitate post hydralazina le alte dosages que esseva usate esseva possibilemente un factor importante in le genese de tal indesirabile reactiones. Pro investigar iste possibilitate un studio "ambi-agnostic" esseva executate in que le patientes recipeva a varie periodos reserpina, reserpina e hydralazina in combination, o un medication fictive, con le administrationes de hydralazina restringite a 300 mg per die o minus. Le resultatos del studio esseva le sequente:

1. Hydralazina in doses diurne de 300 mg o minus, administrate in combination con reserpina, produceva un statisticamente significative effecto hypotensive in le grande majoritate de nostre patientes con hypertension fixe de un durantia de plus que tres annos. Le reduction median del pression sanguinee esseva 44 mm Hg systolic e 25 mm Hg diastolic.

2. Iste grado de efficacia therapeutic esseva obtenite in nostre serie sin le occurrentia de significative formas de toxicitate. Isto es de accordo con le impression que le frequentia de toxicitate es al minus in parte un function del dosage. Assi nos conclude que le campo de utilitate de hydralazina pote esser grandemente extendite si le dose es restringite a nivellos moderate.

3. Reserpina sol produce un significative effecto hypotensive in certe patientes con hypertension fixe e prominente. Le reduction median del pression sanguinee esseva 20 mm Hg systolic e 15 mm Hg diastolic. Iste agente pote essayar se initialmente in patientes hypertensive, con le addition subsequente de hydralazina in doses moderate secundo le grado del responsa therapeutic.

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SIMPLIFIED HEPARIN THERAPY OF IMPENDING AND ACUTE MYOCARDIAL INFARCTION *

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IT is now recognized that premonitory symptoms occur in a substantial proportion of all attacks of acute myocardial infarction.[1] There is a definite change in the clinical picture, with increasingly severe angina and rapidly decreasing effort tolerance. The electrocardiogram at rest may or may not indicate coronary insufficiency, and it is not as important as the clinical story in the diagnosis. This is particularly true when the patient has been under the physician's care for a considerable time. Nevertheless, the diagnosis of impending coronary occlusion cannot be established with absolute certainty unless an infarction actually occurs. It is most apt to be correct when patients with proved coronary disease, as manifested by a previous acute thrombotic episode or by effort angina with positive electrocardiographic findings, experience a sharp symptomatic decline in their clinical picture for several days or weeks. Wright has recently listed such patients as candidates for long-term anticoagulant therapy.[2]

The efficacy of anticoagulant therapy in the prevention of impending myocardial infarction has been reported [3, 4] using oral anticoagulants alone, or after the initial use of heparin for several days.

Because it is considered the most effective anticoagulant, and since it has other actions which might enhance its value, particularly in the hyperlipemic atherosclerotic patient, heparin has been initially given for one to two weeks before the oral anticoagulants were prescribed in a group of 19 patients who fulfilled the criteria of impending myocardial infarction previously described. This longer period of heparinization was made economically and therapeutically feasible by the use of concentrated aqueous heparin administered subcutaneously. Although comparisons are difficult since the criteria for the diagnosis may vary with different investigators, the results in this study, using heparin alone for the first one to two weeks, were apparently superior to those previously reported.[3, 4] In this regard, it is significant that Nichol [5] has noted the clinical impression of his group that the longer heparin is continued in the therapy of impending myocardial infarction before oral anticoagulants are given, the better are the results obtained.

The administration of heparin in our patients has varied somewhat as to dosage and duration of therapy. Aqueous heparin, either 100 or 200 mg. per milliliter, was used, although the more concentrated material is preferable when doses above 200 mg. are given. With a small needle, the drug

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was injected subcutaneously in the relatively insensitive areolar tissue just above or below the posterior iliac crest. Intramuscular injections are to be avoided, as the duration of effect is decreased thereby. Whenever possible, doses of 150 to 200 mg. were administered every 12 hours; otherwise, 300 to 400 mg. doses were given every 24 hours. It has been found that this method of administration usually affords well maintained anticoagulation.[5] It is as efficient as the use of heparin in retarding menstruum,[6, 7] and is less expensive, less painful and less difficult to administer. In several patients an initial dose of 100 mg. was given intravenously. Therapy was continued with heparin alone for one to two weeks (nine and one-half days on the average). Lee-White clotting times were determined at intervals in all cases, primarily to check the adequacy of the dose. When the heparin was administered every 12 hours excellent anticoagulation was maintained in this series. When it was injected every 24 hours, the clotting time, tested 24 hours after the previous dose, was usually at therapeutic levels, except in a few instances, when it was slightly lower. No harm was noted and no particular concern was felt when the coagulation time was prolonged to one to two hours. Jorpes [8] believes these high peaks of anticoagulation are advantageous. We are in agreement with the Scandinavian workers, [6, 9] that it is not necessary to check Lee-White times frequently when heparin is used in this manner. Two of the patients had known duodenal ulcers, but anticoagulant therapy was not withheld and there was no hemorrhage. In two patients mild nasal or hemorrhoidal bleeding occurred, necessitating a slight decrease in the dose of heparin. One patient had moderately severe lumbar pain for several hours after each injection, but no hematuria was found. Oral anticoagulants (Dicumarol or phenylindandione) were started after a good symptomatic response had taken place, and heparin in doses of 200 mg. two or three times weekly was usually continued for two to three months longer. Absolute bed-rest was not prescribed. The patients were initially kept from work but were allowed to be up at home (two were hospitalized for several weeks), with their activity markedly restricted. In some instances the medication was administered at the office, in others, at home.

In all, 19 patients have been treated in this manner. There were 15 men and four women, varying in age from 38 to 74 years. Five had hypertension, three had diabetes mellitus. The results were as follows:

Two patients developed transmural myocardial infarction; one died in the first 24 hours in shock, one survived. Both of these patients had had a rapid increase in their symptoms within the two to three days prior to the onset of therapy.

Four patients had transitory T wave changes with elevated sedimentation rates. They were diagnosed as subendocardial infarction.

Thirteen patients did not develop evidence of infarction while under treatment. Four of the 13 discontinued anticoagulant therapy after two

to four weeks. One of these had an acute transmural infarction 10 days later; a second died suddenly within six weeks; a third developed a small anterolateral infarction within three months.

The percentage of patients developing frank transmural infarcts in this rigidly selected group of known coronary patients with impending myocardial infarction is small. The occurrence of myocardial infarcts in three

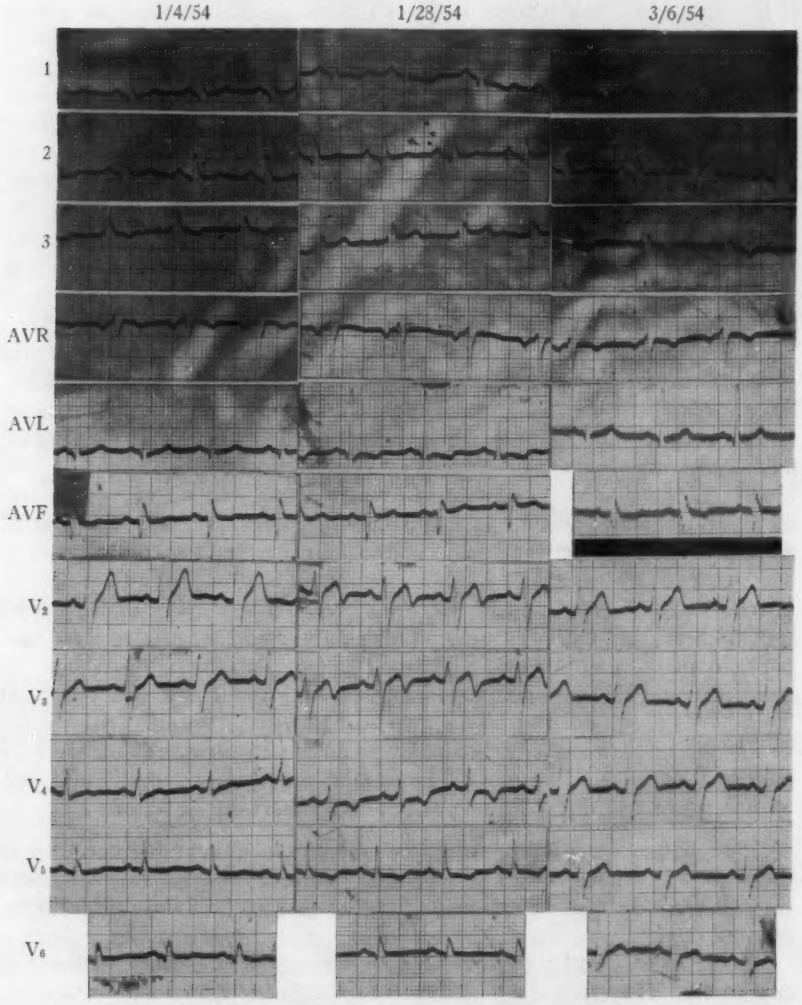


FIG. 1. Electrocardiograms before onset of symptoms of impending infarction, at start of heparin therapy and after five weeks of therapy.

of the four patients who discontinued therapy substantiates the validity of the previous diagnoses. A considerably smaller percentage of the patients in this group had evidence of subendocardial necrosis than in a large series recently reported,[3] in which heparin was given for a shorter time before oral anticoagulants were started. In two of the patients reported in the present series the symptoms of impending infarction, which had developed while they were receiving adequate prophylactic oral anticoagulant therapy, gradually improved on heparin therapy and no infarction occurred. These two cases further suggest that beneficial results may be obtained following the administration of heparin beyond the protection afforded by prothrombin-depressing drugs.

The following case history is illustrative:

Case Report

A 47 year old man had sustained an acute posterior infarction seven years before. He had mild hypertension, which responded well to therapy. His blood cholesterol was 370 mg.%. He had had mild anginal pain after moderate exertion since his coronary occlusion. He followed a prescribed low fat diet rather poorly, received vasodilator drugs, and for one year had been taking phenylindandione, with adequate prothrombin depression. He had been able to carry on his business until one week before he was seen, at which time his activity became markedly restricted by progressively severe angina and night pain. Rest at home brought no great improvement. An electrocardiogram revealed new anoxemic changes in the precordial leads (figure 1). There was no fever, and the sedimentation rate and white blood count were normal. His symptoms began to improve after five days of heparinization, oral anticoagulants were again given after two weeks of daily heparin therapy, and heparin in doses of 200 mg. three times weekly was also continued for another two months. Table 1 shows the serum lipoprotein values (ultracentrifugally determined Standard Sf values in mg.%), and the Lee-White clotting times before and 20 hours after the first dose of heparin. Figure 1 illustrates the electrocardiographic findings in this man prior to the episode diagnosed as impending infarction, the day heparin was started, and one month later. Although such changes can occur spontaneously, there has been similar improvement in anoxic patterns in other patients after several weeks to months of therapy.

Table 1

Lipoprotein Values (Ultracentrifugally Determined Standard Sf Classes in mg.%) and Lee-White Clotting Time Prior to and 20 Hours after the First Dose of Heparin

	Sf 0–12	Sf 12–20	Sf 20–100	Sf 100–400	Lee-White Time
Before Heparin	593	95	221	106	16 min.
After Heparin	694	54	70	0	48 min.

Discussion

It has been generally agreed that if heparin could be administered easily, it would be the preferred anticoagulant.[8, 9, 10, 11, 12] It is a physiologic sub-

stance with a wide margin of safety, acts very quickly and effectively, has few contraindications, and is rapidly neutralized by the injection of protamine sulfate or whole blood. There is excellent experimental evidence that it is more effective than prothrombin-depressing drugs in the prevention of thrombosis, unless the latter drugs are given in doses large enough to lower prothrombin levels dangerously.[13, 14] Wessler,[15] in a study of intravascular coagulation in the isolated venous segments of dogs, found the anticoagulant action of heparin superior to that of Dicumarol. He believed that prothrombin depression provides a less optimal anticoagulant effect than the blocking of fibrin deposition through other mechanisms. More recently he has demonstrated that serum fractions containing Convertin and proconvertin (SPCA) regularly initiate intravascular clotting in the presence of stasis.[16] Heparin effectively inhibited this thrombosis when the clotting time was doubled, whereas when prothrombin activity was lowered, even to dangerous levels, clotting was not prevented. Since excessive SPCA activity has been observed in some clinical states where there is a tendency to thromboembolism, the advantage of heparin over the other anticoagulants is clear. Increased viscosity of the blood is often associated with an accelerated clotting time.[17] Heparin lowers blood viscosity quickly, and the reduction in viscosity persists longer than the decrease in coagulation time.[18] Moolten and his co-workers found that increased platelet adhesiveness occurs regularly for two to three weeks following major surgery, trauma, fracture and pulmonary infarction, and that in myocardial infarction there is a marked increase of platelet adhesiveness which predisposes to thrombosis. Heparin, in doses of 100 mg. intravenously or subcutaneously, caused a prompt lowering of this adhesive tendency, whereas Dicumarol was ineffective despite good hypoprothrombinemia.[19]

Quite apart from its superior efficacy and safety as an anticoagulant, there are many other considerations which indicate that heparin is the drug of choice in the prevention and treatment of thrombotic disease, particularly when atherosclerosis is the basic pathologic lesion. The clearing of alimentary lipemia following the injection of heparin has been known since 1943.[20] Ultracentrifugal studies [21] then demonstrated that lipemic clearing is the result of a shift of serum lipoproteins from larger to smaller particles (figure 1), a process associated with removal of fat from the blood stream. It has only recently been appreciated, however, that alimentary lipemia is associated with increased coagulability of the blood,[22] increased platelet adhesiveness,[23, 24] increased adhesiveness and aggregation of erythrocytes,[25] and an increase in viscosity.[25] A definite deterioration of the ballistocardiogram has also been observed in some patients with angina at the peak of lipemia three hours after a fat meal, not immediately after the meal, when gastric distention is maximal.[26] This observation is in accord with improvements in the ballistocardiogram which have been noted several hours after the injection of heparin.[27] These various harmful effects of serum

lipemia per se are eliminated by the use of heparin but not by the oral anticoagulants, which have no effect upon serum lipids, lipoproteins or lipemia.

Martin and Hueper [28] found that there was a reduction in the speed of oxygenation of the erythrocytes in hypercholesteremic rabbits, and after the injection of macromolecular substances, which they attributed to the formation of macromolecular surface films on the red cells and impaired gaseous exchange across the interface. Within the last year, in a study of forearm arteriovenous oxygen differences in coronary atherosclerotic patients,[29] it was found that the majority of these individuals had low A-V differences which were elevated toward normal several hours after the injection of heparin, but were not affected by Dicumarol or phenylindandione drugs. Studies of total oxygen uptake in these patients (work in progress) are corroborating these observations, indicating a true increase in tissue oxygen consumption in some atherosclerotic individuals after heparin, a process in which the myocardium may participate. The mechanism of this effect may be interference in molecular or gaseous exchange by macromolecular lipid capillary intimal films or red blood cell films,[25, 28] or by lipid inhibition of normal carbohydrate metabolism.[30, 31] Finally, in this enumeration of actions of heparin other than its anticoagulant one, two other observations should be mentioned. Heparin may play a rôle in the normal formation of collagen.[32] It is the only anticoagulant that prevents experimental pulmonary edema.[33] These last two considerations apply less, however, to impending myocardial infarction than to the therapy of acute infarction itself.

In view of the additional advantages which have been presented, and since a simplified method of continuous heparinization with concentrated aqueous material administered subcutaneously is now available,[5] heparin has been used in the manner and dosage described earlier in this paper as the anticoagulant for the first three weeks following acute myocardial infarction in 15 patients. While the group is of course far too small for analysis of results, the therapy is simple and the results are good. One mild episode of oozing of blood from the gums has occurred, and slight temporary loss of hair occurred subsequently in another patient. Only a few Lee-White clotting time determinations are needed to establish the patient's response, in contrast to the frequent prothrombin time tests necessary with all other anticoagulants. Thus the actual saving to the patient with oral anticoagulant therapy is not large. Furthermore, another consideration comes to mind. Recently several observers have questioned the need for anticoagulant therapy in all cases of acute coronary thrombosis,[34, 35, 36, 37] since the risk of death from hemorrhage is greater than the anticipated benefit in mild cases. Others [3, 38] disagree with this point of view, since it is impossible to distinguish all mild cases from the severe ones at the onset of an episode of acute infarction. It has recently been found [39] that in 29% of the cases of acute myocardial infarction the initial classification of the

patient as "mild" or "severe" had to be reversed. These same authors [39] felt: "It is difficult, if not impossible, to form an accurate opinion of the prognosis of myocardial infarction in the early stages." A careful perusal of the report [40] of a survey of 228 specialists' results indicates that, of 223 men who used anticoagulants, only six used heparin alone. Since heparin is usually administered for only two days when oral anticoagulants are used, the great majority of the hemorrhagic deaths, if not all of them, were due to Dicumarol. Although hemorrhage due to heparin occurs, it is usually mild and easily controlled at once by intravenous protamine sulfate. The incidence of hemorrhagic deaths, the core of the argument against the routine use of anticoagulants in acute myocardial infarction, is the result of the widespread use of prothrombin-depressing drugs, not from the use of heparin, which is a safer medication.[8, 9, 11]

Summary

1. The administration has been described of concentrated aqueous heparin subcutaneously for the initial one to two weeks in a group of 19 coronary atherosclerotic patients with an impending myocardial infarction.

2. The results in this series were good: two patients developed an acute transmural infarction, a diagnosis of subendocardial infarction was made in four, and in the other 13 apparently no infarction took place during therapy. Four of these 13 discontinued therapy prematurely, and in three, acute infarction or death occurred within several months.

3. Many other actions of heparin have been reviewed which indicate its superiority over other anticoagulants in the therapy of impending and acute myocardial infarction.

4. In 15 patients with an acute myocardial infarction, continuous anticoagulation has been maintained for the first three weeks, with concentrated aqueous heparin administered subcutaneously every 12 or every 24 hours. This method is simple and economically feasible, and requires few laboratory tests for control.

5. Reasons have been presented indicating that arguments against the routine use of anticoagulants in all cases of myocardial infarction do not apply to heparin.

Summario in Interlingua

Es describite un simple methodo de heparinisation continue in patientes de atherosclerosis coronari con symptomas premonitori de imminente acute infarcimento myocardial. Heparina aquose (in un concentration de 200 mg per cm cubic) esseva administrate subcutaneemente in doses de 150 a 200 mg a intervallos de 12 horas o in doses de 300 a 400 mg a intervallos de 24 horas. Iste programma resulta usualmente in adequate mantenentia del action anticoagulante. Dece-nove patientes esseva tractate in iste maniera durante un a duo septimanas, sequite per 200 mg heparina administrate subcutaneemente inter duo e tres vices per septimana durante plure menses additional. Duo patientes disveloppava infarcimentos transmural, e quatro alteres

habeva infarcimentos subendocardial. Dece-tres patientes non disveloppava infarcimentos durante le curso de heparina. Quatro in iste gruppo de 13 patientes interrumpeva le tractamento post alicun septimanas. Tres de illes habeva un infarcimento intra le sequente tres menses. Iste resultatos es melior que le previemente reportate resultatos obtenite per medio de anticoagulantes oral.

Es presentate un summario de datos in le litteratura que indica que heparina deberea esser le anticoagulante de election, specialmente in patientes atherosclerotic. Heparina es le anticoagulante le plus efficace e le plus secur. Illo reduce le viscositate del sanguine; illo reduce le adhesivitate del plachettas; illo reduce lipemia postalimentari (que promove le tendentia coagulative); illo altera le lipoproteinas seral in le direction del norma; illo inhibi acute edema pulmonar.

A causa de iste avantages, heparina esseva etiam administrate in le maniera describite, durante periodos de tres septimanas, a 15 patientes qui habeva habite acute infarcimentos myocardial. Le therapia es facile a manipular e require multo minus tests laboratorial de controlo que le administration de anticoagulantes oral. Assi le costo del uso de heparina non excede per multo le costo del uso de drogas a depression prothrombinic. Le resultatos in nostre serie, que non esseva extense, ha essite bon. Nulle major hemorrhagias ha occurrite.

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MORTALITY RATES IN ACUTE MYOCARDIAL INFARCTION. IV. THE SEASONAL VARIATION IN MORBIDITY AND MORTALITY *

By Sidney Schnur, M.D., F.A.C.P., *Houston, Texas*

The majority of published studies concerned with the seasonal occurrence of acute myocardial infarction indicate the incidence to be highest in the winter and lowest in the summer.[1, 2, 3, 4, 5] Recently, some doubt has arisen as to whether this characteristic seasonal variation also holds true for southern latitudes. A recent report suggested that in a climate characterized by very hot summer weather "the greatest number of cases occurred in the summer months, and the lowest number of cases in the winter months." [6, 7]

The purpose of this investigation was to determine the experience of this southern community with respect to the seasonal morbidity and mortality from acute myocardial infarction.

Methods of Study

The clinical records of patients admitted to Jefferson Davis Hospital from 1941 to 1952 and to Methodist Hospital from 1945 to 1952 were reviewed and only those records were selected for this study which indicated unequivocal evidence of acute myocardial infarction. A total of 930 records was considered acceptable, and these were classified according to the month and season of occurrence of the disease.

The number of deaths from acute myocardial infarction reported to the Houston Health Department from 1947 to 1952 totaled 3,971. These were classified according to the month and season in which death occurred.

Results

Figure 1 presents the number of admissions for each month of the year, and figure 2 the admissions classified according to seasons of the year. The largest number of admissions (268 patients, or 28.8%) occurred during the winter months,† whereas the smallest number (216 patients or 23.2%) occurred in the summer.‡

Figures 3 and 4 graphically present the number of deaths from this disease which occurred during each month and season of the year. The results appear to confirm the findings relating to "incidence," i.e., the largest

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† S.E. = 2.5 ($P < .01$).

‡ S.E. = 1.4 (not statistically significant).

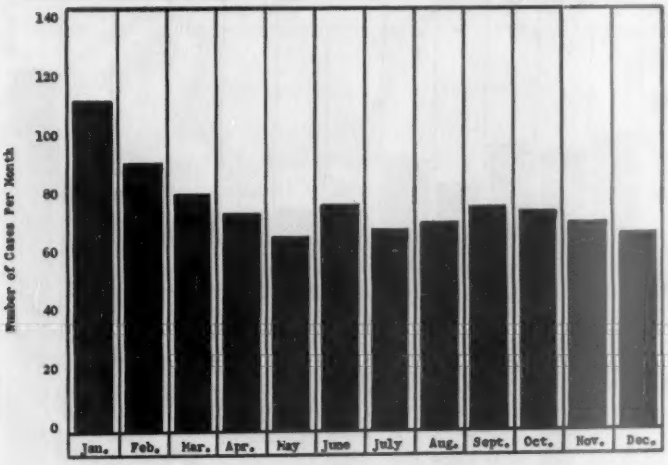


FIG. 1. Hospital admissions for acute myocardial infarction classified according to months of the year.

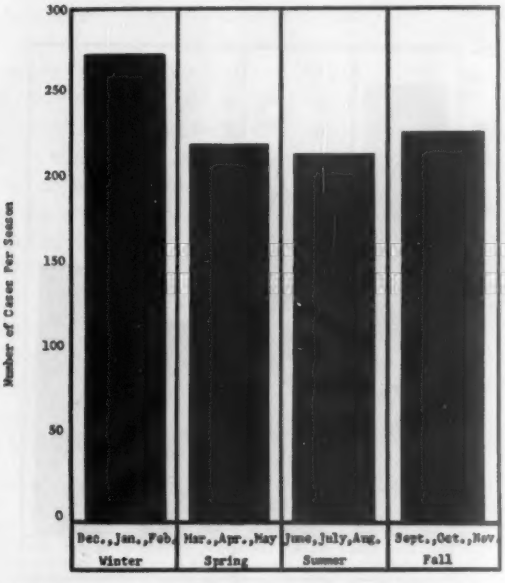


FIG. 2. Hospital admissions for acute myocardial infarction classified according to seasons of the year.

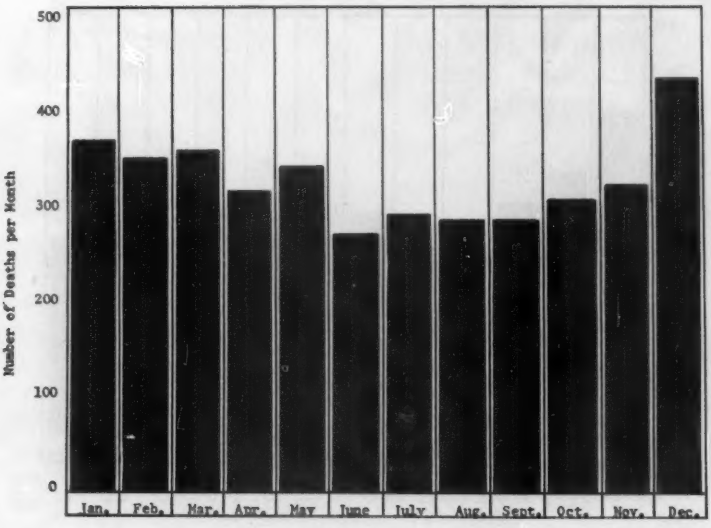


FIG. 3. Deaths from acute myocardial infarction in Houston from 1947 to 1952 classified according to months of the year.

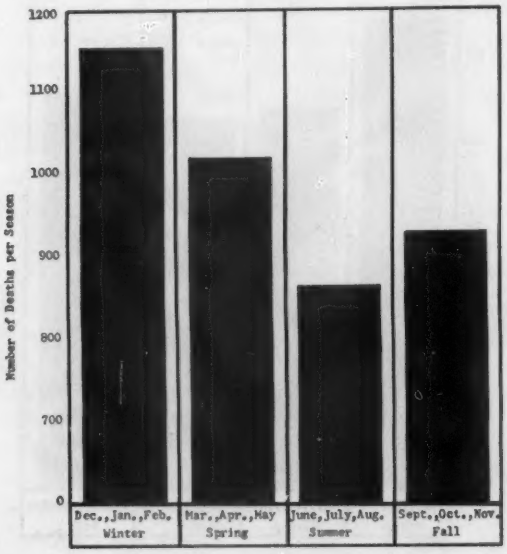


FIG. 4. Deaths from acute myocardial infarction in Houston from 1947 to 1952 classified according to seasons of the year.

number of deaths was reported in the winter (1,159, or 29%) and the smallest number in the summer (876, or 22%)—a significant difference.

Discussion and Conclusions

Conclusions regarding disease incidence derived from this as well as most other investigations of this problem can be accepted only with reservations, owing to the questionable design of these studies. First, hospital admissions do not necessarily accurately reflect disease incidence. Actually, the correct determination of incidence is made by adding the total number of patients hospitalized for a disease to the total treated at home and dividing the sum by the total population of the community during the period of survey. Hospital admissions therefore comprise but one of the three variable factors in the computation, the others being uncontrolled and subject to change.* Second, broad generalizations concerning the incidence of disease in large sections of the country are not completely valid when based upon admissions during a period of a few years of a relatively small number of patients to two or three hospitals in a single community. Larger and more diversified samples are required to neutralize or dilute significant but generally unrecognized extraneous factors which may affect admissions to specific hospitals and which may be unusually potent in a particular community, hospital, season or year. An example of such potential source of error is the presence or absence of air-conditioning in a hospital. During the summer in the South, patients will invariably first request admission to a hospital providing this comfort, and only if a bed is not available will they accept a non air-conditioned hospital. This shifting summer preference, which is determined solely by the type of physical plant, may result in an "above average incidence" in one hospital and a "below average incidence" in another hospital in the same community during the same season.

The results of this investigation indicate that in the two hospitals studied in this city more patients with acute myocardial infarction were admitted in the winter than at any other season of the year. This confirms the personal opinion of local hospital admitting personnel who have learned to provide additional beds for expected "coronaries" whenever the local weather bureau forecasts a blue norther, i.e., a severe cold front from Canada or the Rockies which generally causes a precipitous drop in temperature, averaging 20 degrees, with extremes of 5 to 40 degrees.† Over 80% of these dis-

*The population factor would be especially significant in certain industrial and agricultural communities where employment is seasonal, and in popular resort areas where differences in hospital admissions may actually reflect fluctuations in population rather than a seasonal variation in the "incidence" of disease.

† Statistical data are not available to support this observation since this study was not designed to determine the relationships between specific meteorological phenomena and the occurrence of myocardial infarction. Nevertheless, the opinion of most experienced clinicians in this community is that sudden temperature changes during any season but especially a precipitous drop in the winter and a rapid rise in temperature and humidity in the summer not infrequently are associated with increased hospital admissions for this disease.

turbances occur during the three winter months. The seasonal variation in the number of deaths from this disease reported to the Houston Health Department also appears to support indirectly the findings of a high winter and low summer incidence.‡ The experience of this southern community is therefore quite similar to that reported from cities located in the northern latitudes and does not confirm the presence of a "reversed" seasonal incidence in the South.

Summary

1. A study of 930 patients with acute myocardial infarction admitted to two hospitals in this southern city revealed that a significantly greater number of patients with acute myocardial infarction were hospitalized in the winter than in any other season of the year.

2. An analysis of 3,971 deaths from acute myocardial infarction reported to the Houston Health Department from 1947 to 1952 disclosed that the largest number (29%) occurred during the winter months and the smallest number (22%) during the summer.

3. These findings, which indicate that both the incidence and the number of deaths are highest in the winter, confirm earlier reports from various sections of this country, and do not support the contention of a "reversed" seasonal incidence of this disease in the South.

Acknowledgment

The author is grateful to Dr. W. G. Glass and Dr. Ray W. Goens for their assistance in obtaining some of the data included in this report, to Mr. Howard J. Stroud and Mr. William H. Albans, of the Houston Health Department, for the vital statistics, and to Mr. T. R. Swaim, of the U. S. Weather Bureau, for the meteorologic information.

Summario in Interlingua

Le majoritate del publicate studios del occurrentia saisonal de acute infarcimento myocardial indica que le frequentia del morbo attinge su maximo in hiberno e su minimo in estate. Un recente studio del admissiones a plure hospitales in un citate del sud del Statos Unite pareva indicar que le mentionate variabilitate saisonal es revertite sub conditiones de climate calide.

Le presente investigation esseva interprendite pro determinar si le mesme phenomeno es characteristic del situation in altere communitates del sud del Statos Unite e etiam pro criticar le plano de studios del frequentia de un morbo in tanto que tal studios es basate exclusivemente super le statistica del admissiones hospitalari.

Le casos de 930 patientes admittite con acute infarcimento myocardial a duo hospitales in le curso de plure annos e 3971 casos mortal del morbo in le archivos del Departimento de Sanitate de Houston, Texas, esseva analysate e classificate secundo le mense de lor occurrentia. Cira 29 pro cento del admissiones e mortes occurreva durante le menses del hiberno e 23 pro cento durante le estate. Iste resultatos confirma previe reportos ab varie sectiones del pais que le frequentia del morbo ha su maximo in hiberno e su minimo in estate; illos non supporta le assertion que le distribution saisonal del morbo es "revertite" in le sud.

‡ This would be true if the mortality rate remained constant throughout the year. If the rate were higher during the winter because of associated respiratory disease etc., some of the deaths might be attributable to this factor rather than to an increased number of cases.

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DISCOID LUPUS ERYTHEMATOSUS: AN ANALYSIS OF ITS SYSTEMIC MANIFESTATIONS *

By Edmund L. Dubois, M.D., *Los Angeles, California,* and Stuart Martel, M.D., *Whittier, California*

Although it is generally accepted that the various forms of lupus erythematosus are merely different manifestations of the same disease, the most common variety, namely, the chronic discoid form, has been regarded as primarily a localized manifestation whose systemic changes are either absent or missed. The object of this study is to point out that these generalized changes are very common in discoid lupus and have hitherto been overlooked.

Chronic discoid lupus is characterized by skin lesions which in the active phase consist of erythematous plaques of varying sizes with scaling, follicular plugging, followed in the healing stages by atrophy and either depigmentation or hyperpigmentation. O'Leary has divided these cases into two groups, the localized or chronic discoid form, where the lesions are confined to the face, ears, scalp and lower lip; and the generalized discoid form, which is also referred to as the chronic disseminated form, in which the lesions, in addition to the above site, may be present elsewhere on the body.[1] This arbitrary differentiation was rigidly adhered to in this paper, so that if a patient at some time in the course of the illness had a single cutaneous lesion below the chin, she was classified with the generalized discoid group.

Other workers have pointed out the occasional occurrence of systemic manifestations in discoid lupus.[2, 3, 4] Wilson and Jordan even suggested that discoid lupus is a systemic disease from its inception.[5] To the best of our knowledge, no author has gathered a group of patients with chronic discoid lupus and carefully interviewed them, utilizing a questionnaire with particular emphasis on the clinical course of their illness and the systemic changes which they might have noted during it. This is the method we employed. Each patient had, in addition, a complete physical examination at the same time. The tabulating form we used was enlarged from one used by one of us (E.L.D.) in a previous study of the manifestations of systemic lupus erythematosus in a series which now numbers 150 cases.[6] The patients described in the present paper were attending dermatology clinics and had had a diagnosis of chronic discoid lupus made by competent dermatologists either by the clinical appearance or by biopsy of the lesion, or both. Patients with discoid-type lesions and compatible biopsies who had obvious disseminated disease, with fever, severe arthritis, anemia and other changes

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TABLE 1

Clinical Data on 41 Cases of "Discoid" Lupus Erythematosus Compared to a Series of Systemic Cases [6]

	No. of Cases	Range	Median	Mean
Ages of Onset (Years)				
Localized discoid	26	9–60	32	34.3
Generalized discoid	15	11–53	33	31
Systemic	62	2–67	24.2	23.7
Ages of the Patients (Years)				
Discoid series	41	14–63	40	41.5
Systemic series	62	2–67	26.6	27.5
Duration of Disease (Months)				
Localized discoid	26	1–312	66	98
Generalized discoid	15	15–300	98	116
Total discoid group	41	1–312	90	107
Systemic series	62		28.5	45.1
Duration of Antimalarial Therapy (Months)				
Localized discoid	22	1–32	10	14
Generalized discoid	14	3–23	13	11.5
Total discoid group	36	1–32	10	12.7

TABLE 2

Clinical Data on 41 Cases of "Discoid" Lupus Erythematosus Compared to a Series of Systemic Cases

	Group of 26 Cases Localized Discoid		Group of 15 Cases Generalized Discoid		Total Group of Cases of Discoid L.E.		Systemic L.E. 62 Cases
	No.	%	No.	%	No.	%	%
Females	18	69	11	73	29	71	89
White	13	50	8	53	21	51	47
Negro	10	38	7	47	17	41	19
Mexican*	3	12	0		3	7	29
Spontaneous remissions of skin lesions	1	4	3	20	4	10	†
First system involved							
Arthritis	5	19	2	13	7	17	34
False-positive serology	0	0	1	7	1	2	3
Discoid lesions	21	81	12	80	33	71	16
Evidence of systemic change as determined by history and physical examination	16	62	14	93	30	73	100
Evidence of systemic change as determined by history, physical and laboratory examination	29	92	15	100	39	96	100

* The incidence of discoid disease is very much lower in this group than in the hospital population.

† The over-all systemic spontaneous remission rate for all systems involved is 40%. There was a similarly high spontaneous remission rate for the systemic symptoms which appeared in the patients with "discoid" lupus.

typical of acute disseminated lupus concurrent with the onset of their cutaneous lesions, were not included in this series. Forty-one patients were selected as outlined above. Twenty-six had the localized discoid form and 15 the generalized discoid form. Routine laboratory work, liver function tests, heparinized L.E. cell preparations, skin biopsies and electrocardiograms were obtained on most of the patients.

Clinical Features

The detailed clinical features are presented in tables 1 through 4, where their incidences are compared to those found in a series of 62 cases with

Table 3

Symptoms and Signs of 41 Cases of "Discoid" Lupus Erythematosus Compared to a Series of Systemic Lupus Erythematosus

	Group of 26 Cases Localized Discoid L.E.		Group of 15 Cases Generalized Discoid L.E.		Total Group of 41 Cases of Discoid L.E.		Systemic L.E.[a] 62 Cases
	No.	%	No.	%	No.	%	%
Active skin lesions	26	100	15	100	41	100	84
Atrophy at site of skin lesions	19	73	12	80	31	76	
Photosensitivity	16	62	11	72	27	66	40
Rheumatoid arthritis	13	50	10	67	23	56	90
Weight loss	8	31	5	33	13	32	82
Acute chronic rheumatoid deformity	6	23	5	33	11	27	31
Pleurisy	4	15	6	40	10	24	60
Diffuse alopecia	5	19	5	33	10	24	70
Fever	5	19	4	27	9	22	97
Raynaud's phenomenon	5	19	3	20	8	20	35
Nausea	4	15	2	13	6	15	36
Abdominal pain	4	15	1	7	5	12	42
Vomiting	3	12	1	7	4	10	40
Pericarditis	4	15	0	0	4	10	44
Mucous membrane lesions	2	8	2	13	4	10	11
Adenopathy	3	12	0	0	3	7	42
Heart murmurs	1	4	1	7	2	5	42
Diarrhea	1	4	1	7	2	5	37
Myocarditis	1	4	0	0	1	2	17
Hepatomegaly	0	0	1	7	1	2	34

None of the patients in the "discoid" group had pleural effusions, ascites, fundic lesions, convulsions, psychoses, central nervous system damage or splenomegaly, all of which are frequently encountered in systemic L.E.

systemic lupus erythematosus studied at this hospital several years ago or in other similar series. The sex ratio was 71% female in the discoid group, as compared to 89% in patients with systemic disease. The median age of onset is 32 years in the discoid group versus 24 years. The disease appeared in both the localized and the generalized discoid group at about the same ages. Complete spontaneous remission in the skin lesions occurred in only four patients, although remissions in their systemic complaints were

very frequent. The spontaneous over-all remission rate in systemic lupus erythematosus is about 40%.

There were three modes of onset of discoid lupus in this series: Thirty-three patients (or 71% of the group) had the textbook pattern of cutaneous changes. Arthritis of the rheumatoid type was the presenting symptom in seven cases (ages 14, 20, 29, 31, 35, 48 and 60 years), or 17%. Five of these patients had localized discoid-type lesions, and the other two had the generalized discoid form. One patient had a false-positive serologic test for syphilis as her first change produced by the disease, followed by discoid lesions several years later.

TABLE 4

Laboratory Data on 41 Patients with "Discoid" Lupus Erythematosus Compared to the Systemic Form

	Cases Studied	No. Positive	Per Cent
Hemoglobin (below 12 gm.)			
Localized discoid group	26	3	12
Generalized discoid group	15	9	27
Total discoid group	41	7	17
Systemic[8]	323	258	80
Leukopenia (WBC below 5,000 before therapy)			
Localized discoid group	24	8	33
Generalized discoid group	15	8	67
Total discoid group	39	16	41
Systemic[9]	109	78	72
Leukopenia (WBC below 5,000 during therapy)			
Localized discoid group	20	9	45
Generalized discoid group	15	7	47
Total discoid group	35	16	39
Sedimentation Rate (Wintrobe) Positive test = {Abnormal for males over 9 mm./hr. {Abnormal for females over 20 mm./hr.			
Before therapy			
Localized discoid	19	17	90
Generalized discoid	13	9	69
Total discoid	32	26	82
Systemic[8]	245	218	89
During therapy			
Localized discoid	12	9	75
Generalized discoid	9	7	78
Total discoid	21	16	76
L.E. Cells[12]			
Localized discoid	24	2	8
Generalized discoid	14	1	7
Total discoid group	38	3	8
Systemic[6]	60	41	69
False-Positive Serologic Tests for Syphilis			
Localized discoid	23	3	13
Generalized discoid	15	1	7
Total discoid group	38	4	10
Systemic[6]	62	19	33
Serum Globulin (over 2.5 gm. % abnormal in 95% of cases at this laboratory)			
Localized discoid	17	7	41
Generalized discoid	10	5	50
Total discoid group	27	12	45
Systemic[10]	105	61	58

TABLE 4—*Continued*

	Cases Studied	No. Positive	Per Cent
Cephalin-Cholesterol Flocculation before Therapy			
Localized discoid group ($3–1^+$, $2–2^+$, $1–4^+$)	11	6	55
Generalized discoid group ($2–1^+$, $1–2^+$, $1–3^+$)	6	4	67
Total discoid group	17	10	59
Systemic (10)	82	67	82
Cephalin-Cholesterol Flocculation during Therapy			
Localized discoid group ($3–2^+$)	10	3	30
Generalized discoid group ($2–1^+$, $2–2^+$)	5	4	80
Total discoid group	15	7	47
Thymol Turbidity			
Before Treatment (over 5U)			
Localized discoid	10	4	40
Generalized discoid	6	4	67
Total discoid group	16	8	50
Systemic[10]	82	67	82
During Treatment			
Localized discoid	8	2	25
Generalized discoid	5	1	20
Total discoid group	13	3	23
Bromsulphalein Test (during Therapy)	10	0	0
Urinalysis (abnormal tests)			
Localized discoid	25	2	8
Generalized discoid	15	1	7
Total discoid group	40	3	8
Systemic[6]	62	35	57
Electrocardiographic Abnormalities Due to Systemic L.E.			
Localized discoid group	15	2	13
Generalized discoid group	10	1	10
Total discoid group	25	3	12
Systemic[6]	62	23	37
Skin Biopsy	37	36	97
Results of Antimalarial Therapy			
Localized discoid: Completely healed	22	14	64
Markedly improved	22	8	36
Generalized discoid: Completely healed	14	4	29
Markedly improved	14	10	61
Total discoid group: Completely healed	36	18	50
Markedly improved	36	18	36

The first case illustrates the typical clinical pattern of localized discoid lupus found in this study. In this patient the rheumatoid arthritis, which is often overlooked because of its mildness, followed shortly after the appearance of the cutaneous changes.

CASE REPORTS

Case 1. A 28 year old white housewife had been in good health until July, 1951, when an eruption appeared on both cheeks which was diagnosed by a dermatologist as discoid lupus. She was treated with gold injections, vitamins and liver injections, without results. In November, 1951, arthralgia appeared in the hands, as well as intermittent pleuritic pains. She was initially examined by us on December 8, 1952, and at this time the skin lesions were typical localized chronic discoid lupus. Al-

though arthralgia of the hands was present there were no rheumatoid deformities. The remainder of the physical examination was normal. Laboratory studies revealed a white cell count of 4,100, with 36% polymorphonuclear cells, 46% lymphocytes, 9% juveniles, 6% monocytes and 3% eosinophils. Wintrobe sedimentation rate, 38 mm. per hour. Albumin, 4.4 gm.; globulin, 3.5 gm. Urinalysis, normal. Peripheral blood L.E. preparation, negative. Skin biopsy was interpreted as chronic discoid lupus. The patient was placed on atabrine, 300 mg. per day. Within several weeks the joint pains disappeared for the first time, as did the skin lesions.

Fifteen of the 33 patients who had cutaneous lesions as their initial manifestation later developed rheumatoid arthritis. Eight of these had only localized discoid lesions, whereas the other seven had the generalized discoid form. The arthritis in the majority of cases occurred within several years of the appearance of discoid cutaneous change, but in one instance it occurred 23 years later.

The second most frequent mode of onset was the appearance of rheumatoid arthritis for some time prior to the discoid lesions. This pattern of development is the most common in systemic lupus erythematosus, where 34% have initial joint involvement. The following patient had rheumatoid-like arthritis for two years prior to the skin lesions of localized discoid lupus erythematosus.

Case 2. A 40 year old white woman complaining of skin lesions of discoid lupus was first examined in September, 1953. She had been in good health until age 14 when intermittent arthritis appeared in the wrists and knees and, in recent years, in the lumbar area. There never was overt evidence of joint inflammation. When she was 16 years of age, after a great deal of sun exposure, a rash of the discoid type appeared on the bridge of the nose. Since then, new lesions had appeared and old ones had healed. She was treated with gold injections, bismuth injections and quinine, without success.

Physical examination revealed an obese, 40 year old woman who appeared several years older. The vital signs were normal. The significant findings were classic active and healed discoid-type lesions on the cheeks and left ear. The remainder of the physical examination was within normal limits. There was no rheumatoid deformity. Hemogram, normal. Wintrobe sedimentation rate, 21 mm. per hour. Urinalysis, normal. Albumin, 3.2 gm.; globulin, 3.8 gm. Peripheral blood L.E. preparation, negative. The patient was placed on atabrine, 0.4 gm. per day, and within three days there was less erythema. Ten days after the start of atabrine therapy her arthritic pains completely disappeared and did not return for 18 months, while she was on maintenance therapy. Within two months the rash fully cleared for the first time in 23 years. On several occasions the patient discontinued her medication, and each time there was a slight cutaneous relapse and recurrence of joint pain, both of which responded within a few days to reinstitution of antimalarial therapy.

The third mode of onset was the appearance in one patient of a false-positive serologic test for syphilis, followed by generalized discoid skin lesions several years later. The pattern may actually have been more common than we found, but due to our inability to obtain treponemal immobilization tests on all cases, many doubtful examples were discarded.

Case 3. A 44 year old white woman, a physician's wife, first examined on June 4, 1953, complained of a rash on her face of three years' duration. The patient had been in good health until 1947, when a routine serologic test for syphilis was found to be positive. Spinal fluid examination was negative. Previous serologic tests had been negative. She received a course of penicillin, and since then her serologic tests often varied from positive to negative. In February, 1950, classic discoid lesions, proved by biopsy, appeared on the cheeks and on the bridge of the nose. She received bismuth and gold injections, without help. In June, 1952, arthritis appeared in the proximal interphalangeal joints with acute inflammatory changes. Five months later she was hospitalized and given ACTH and cortisone therapy over six weeks, with improvement. After stopping the cortisone the patient developed pleurisy and pneumonia. Subsequently the eruption gradually relapsed and spread to her arm, but none of her other symptoms recurred.

Physical examination revealed a well developed and poorly nourished 44 year old white woman in no distress. Vital signs were normal. There were scaling, erythematous discoid lesions on the bridge of the nose, and also a few patches scattered on the extensor surfaces of the elbows and dorsa of the hands. Atrophic lesions of similar size were present on the cheeks. There was a slight degree of fusiform thickening of the proximal interphalangeal joints.

Laboratory studies revealed a normal hemogram, sedimentation rate and urinalysis. L.E. preparation, negative. Kahn, doubtful; Kolmer, 2 plus.

The patient was treated with atabrine. Within several weeks the skin was clear. After six weeks of therapy the serologic tests for syphilis became negative.

Cutaneous Manifestations

The eruptions were classic discoid lupus lesions. Thirty-seven patients had skin biopsies which were interpreted by two pathologists as compatible with chronic discoid lupus erythematosus. The biopsy is of little help in differentiation of types, because a long-standing scaling scarred lesion from a case of acute systemic disease will appear the same as the chronic discoid lesions, whereas a specimen from a fresh discoid lesion often resembles that taken from acute systemic eruptions.[7]

Twenty-seven patients (66%) noted a flare-up of their lesions when they were exposed to sunlight. The systemic changes often were aggravated when the skin lesions flared up. As one patient succinctly stated, "When my lupus is bad my joints are bad. When my lupus gets better the joints get better."

Diffuse partial alopecia was present in 10 patients (24%). This does not include those who had patchy alopecia at the sites of their atrophic lesions. In the systemic form, 70% develop similar thinning of their hair.

Systemic manifestations may appear years after the skin lesions are healed without a relapse in the cutaneous changes (see case 6 below).

Miscellaneous Findings

Table 2 lists the symptoms and signs which we found associated with the underlying disease. Fever was present in nine cases. It usually was low grade and associated with marked activity of the cutaneous lesions or

definite evidence of systemic change, such as arthritis. Thirteen patients (or 32%) lost weight when the skin lesions were active. Ten patients (or 24%) had had intermittent attacks of pleuritis lasting days or weeks. Four patients had symptoms of recurrent pericarditic pain. Electrocardiograms were done in two of these and in one it confirmed the clinical suspicion of pericarditis. One patient (case 6) who had developed disseminated disease had evidence of myocarditis clinically and electrocardiographically. Two patients had systolic heart murmurs, both of which may have been functional.

Three of five patients who complained of bouts of severe abdominal pains in varied locations in the abdomen had advanced systemic changes.

Eight patients had Raynaud's phenomenon develop some years after the onset of their disease. Only two of these patients (cases 6 and 7; see case reports below) had evidence of much generalized extension of their disease.

Rheumatoid Arthritis

Twenty-three patients (or 56%) had arthralgia and arthritis of the rheumatoid type. The incidence was 50% of the localized discoid group and 67% of the generalized discoid group. In some, the pains which were most commonly present in the proximal interphalangeal joints were mild, without gross inflammatory changes in the joints during the acute phases. The attacks of joint involvement lasted days to months at a time. In many of the patients the arthritis was severe enough to warrant their attendance at other clinics in the hospital for relief of their symptoms. Eleven patients had typical rheumatoid deformities of the acute type, with fusiform swelling, and some of this group had a persistent deformity. None had the advanced changes of marked arthritis deformans.

Laboratory Changes

Table 4 lists the results of these studies. Anemia was absent unless there was marked systemic change, in contrast to the typical systemic disease, where 80% have hemoglobins below 12.0 gm.[8] White blood counts were performed in 39 cases, and in 14 of these (or 36%) the lowest pretreatment count was below 5,000 per cubic millimeter. After antimalarial therapy, counts were available in 35 cases, and 16 of these (or 46%) were below 5,000. In many instances, particularly in patients who had been seen only a few times before therapy was instituted, more leukocyte counts were available while under treatment, so that the latter figure of 46% leukopenia is probably a more valid one. Seventy-two per cent of a comparable systemic series had leukopenia.[9] Because of the inherent tendency to leukopenia in the disease itself, in no case was it found necessary to stop antimalarial therapy for this reason. The lowest count was 2,500 in a patient under treatment, with 54% polymorphonuclear cells and a normal

number of platelets. In general, the counts would vary in a range of 1–2,000 cells from baseline levels during treatment.

Four patients had definite false-positive serologic tests for syphilis, three of whom had localized lesions. Many patients had a vague history of syphilitic contact and therapy. We were unable to obtain treponemal immobilization tests in all these cases in order to assess their status correctly.

Serum proteins were done by the Howe separation biuret technic. The serum albumins were normal in all but one case. At this laboratory 90% of the normal globulins are below 2.5 gm.%. Forty-one per cent of the localized discoid group and 50% of the generalized group were above this level, compared to 58% of a systemic group.[10]

Slight abnormalities were found in the liver function studies. Cephalin-cholesterol flocculation was positive in 10 of 17 cases in which it was done. Eighty-two per cent of systemic lupus erythematosus cases have positive tests.[10] Four of seven patients who had a negative test had arthritis, and six of 10 with a positive test had arthritis. However, the arthritic changes were more marked in the latter group. The thymol turbidity test followed a similar pattern.

The Bromsulphalein test (5 mg. per kilogram) drawn at 45 minutes was reported by the laboratory as below 10% (no specific figures given) in nine out of 10 cases. It is felt by most workers that the usual normal is less than 5% at 45 minutes. Therefore, the only assumption that can be made is that this test was not grossly abnormal.

Three patients had evidence of lupus nephropathy, and each of these had clinical evidence of dissemination. Thirty-seven cases had normal urinalyses.

Three patients had evidence of myocardial damage not due to associated diseases. All were patients with other evidences of dissemination. Two had changes of pericarditis (cases 7 and 5) and one of myocarditis (case 6). In 22 others the tracing was either normal or showed secondary changes from other diseases.

Sedimentation Rate

Cochrane found elevated sedimentation rates in 80% of discoid cases.[11] Eighty-two per cent of this series had abnormal rates (a median of 25 mm. per hour Wintrobe in the untreated cases). Eighty-nine per cent of systemic cases have elevated rates. In general, the higher the figure, the more extensive the systemic change in our patients. Only four untreated patients had normal rates. Three of these had generalized lesions. With therapy the sedimentation rate tended to fall toward normal, decreasing an average of 8 mm. per hour.

L.E. Cells

L.E. cell tests were performed in 38 cases by the heparinized technic described by one of us.[12] Three patients had positive tests. At this time

they had evidence of a great deal of systemic involvement. In two of these individuals the skin lesions were limited to the localized discoid type. These cases will be briefly summarized. The L.E. test is usually positive in from 70 to 80% of disseminated lupus cases.

The first patient shows the development of systemic lupus erythematosus with L.E. cells 10 years after the appearance of localized discoid lesions.

Case 4. A 28 year old white male salesman was seen on October 28, 1954, complaining of lupus of 12 years' duration. He had been in good health until 16 years of age, when classic discoid-type lesions appeared on his right cheek and gradually spread over most of that area. He was given the usual therapy with gold, bismuth, etc., without any results. During October, 1952, the first evidence of systemic changes appeared, namely, arthralgia in the right knee followed by weight loss, anorexia, nausea, leg edema and the appearance of L.E. cells. He was hospitalized and given cortisone, with good results. Since then he has been on maintenance cortisone. Because of the appearance of several convulsions he was referred for study.

Physical examination revealed a well developed and well nourished, weak, chronically ill 28 year old male with normal vital signs. The only significant physical findings were partially healed discoid lupus lesions on the right cheek, with hyperpigmentation, slight erythema and scaling, and some atrophy.

Laboratory studies revealed a hemoglobin of 13.4 gm. and a white blood cell count of 4,500, with a normal differential. Wintrobe sedimentation rate, 17 mm./hr. A peripheral blood L.E. preparation was negative at this time. Urinalysis revealed a specific gravity of 1.025 with 1 plus albumin and an occasional red cell per high power field, with occasional hyaline and coarse granular casts.

The second patient developed systemic manifestations and L.E. cells three years after the appearance of her discoid lesion.

Case 5. A 36 year old Negro female was first seen by the authors in April, 1953. At the age of 16 she had had syphilis and had been treated adequately with heavy metals. In 1949 she complained of eructation and vague abdominal pains. Her serologic tests for syphilis were still positive, and she received bismuth injections. At the site of one of these injections a plaque of biopsy proved discoid lupus appeared. In February, 1952, the patient developed circinate plaques on her cheeks, with follicular plugging, atrophy, erythema and a keratotic surface. Biopsy again confirmed the diagnosis of discoid lupus. Several months later arthralgia appeared for the first time in the elbows, wrists, hips and knees. Recurrent bouts of iritis appeared at this time. She also noted transitory tender nodules on the dorsum of her hands which lasted a few days at a time. Because of a persistence of all her symptoms she was admitted for study. The patient was a well developed and fairly well nourished Negro woman with discoid lupus lesions on her cheeks as described above. Slight spindle-shaped swelling of the proximal interphalangeal joints was present. Temperature varied between 99° and 100° F. Laboratory studies revealed a hemoglobin of 10.0 gm., with white cell count of 5,450 and a normal differential. Sickle cell preparations, negative. Urinalysis, normal. Sedimentation rate, 58 mm. per hour (Wintrobe). Gall-bladder and upper gastrointestinal x-ray examinations were negative. Albumin, 3.9 gm.; globulin, 3.7 gm. per 100 ml. Peripheral blood L.E. cell preparation was positive.

The patient was placed on atabrine and within a few days her joints began to improve, and over the next few weeks the erythema of the skin lesions cleared.

The third patient developed arthritis first, followed by discoid lesion five years later. At the time L.E. cells were found there were many evidences of system change.

Case 6. A 39 year old Negro housewife had been in good health until 1943, when she developed lower abdominal pain due to pelvic inflammatory disease, and both she and her husband were found to have syphilis, for which they were treated adequately. The following year one tube and ovary were removed, and since then she had not regained her strength. In 1946 intermittent arthralgia appeared in the ankles, with swelling, which persisted. The following year an acute iritis appeared for several weeks. In 1951 the arthralgia began to involve both knees. The next year typical discoid plaques appeared on the scalp with alopecia. These were 1.5 cm. in diameter, discrete, atrophic, erythematous plaques with follicular plugging. The diagnosis of chronic discoid lupus was confirmed by biopsy. In 1953 the arthritis began to involve the proximal interphalangeal joints and Raynaud's phenomenon appeared. In January, 1954, the patient was seen in the Arthritis Clinic, where a diagnosis of rheumatoid arthritis was made and she received gold injections. One month later we examined the patient and found her to be a well developed and poorly nourished Negro female who showed evidence of much recent weight loss. The scalp lesions had healed at this time. Scattered cervical nodes, 1 to 2 cm. in diameter, were present, and there were several in the axillae. The heart was normal in size, with a grade 3 aortic systolic murmur. There was marked acute swelling of the proximal interphalangeal joints. Knees and ankles were hot and tender.

Hemogram and urinalysis were normal. Serologic tests for syphilis were positive, with a positive Wassermann test in a 1/40 dilution and a positive Kahn in a 1 to 20 dilution. The treponemal immobilization test was negative, suggesting that the patient now had a biologic false-positive test. Wintrobe sedimentation rate, 45 mm. per hour. The electrocardiogram revealed evidence of myocardial damage. The L.E. cell preparation was positive.

Since the patient could not tolerate atabrine and chloroquine because of gastrointestinal toxicity, she was placed on cortisone, with good clinical improvement.

Dissemination of the Disease in Patients with Proved Discoid Lupus and Negative Studies for L.E. Cells

The entire classification of lupus erythematosus is arbitrary. There are no fixed lines of demarcation between the types. In fact, there are transition forms between so-called discoid lupus, generalized discoid lupus, and the subacute and acute disseminated forms. One type often tends to merge into another. Three patients had advanced systemic disease despite the mere presence of so-called discoid lesions confirmed by biopsy. As many as 10 L.E. cell examinations by different technics were performed on each of these patients without a single positive test. The following case illustrates this pattern.

Case 7. A 33 year old Negro woman had been in good health until April, 1951, when red pimples appeared about the bridge of her nose and chin, aggravated by sunlight. With healing, hyperpigmentation appeared. Two months later the patient developed anorexia and a weight loss of 17 pounds, although at this time the skin was fully healed. In September, 1951, arthralgia appeared in the proximal interphalangeal joints, shoulders and wrists. Two months later Raynaud's phenomenon

appeared, and in December, 1951, generalized partial alopecia began. During March, 1952, pericarditic pain was present, and the following month, because of left lower quadrant abdominal pain and distention without bowel movements, she was hospitalized.

The patient was an acutely and chronically ill 28 year old Negro female with a temperature of 103° F. Hyperpigmented, brownish black, depressed atrophic scars with erythematous elevated margins and marked follicular prominence were found scattered on the bridge of the nose, earlobes and chin. A small left pleural effusion was present, as well as a pericardial friction rub. The abdomen was distended, with direct and rebound tenderness, but good bowel sounds were present.

Laboratory studies revealed a hemoglobin of 11.5 gm. and a white cell count of 8,800, with normal differential. Sickle cell preparation, negative. Urinalysis, normal. Skin biopsy was interpreted as showing chronic discoid lupus. One bone marrow and a total of nine peripheral blood L.E. preparations were negative.

The patient was placed on intravenous ACTH, with dramatic benefit, and later was changed to maintenance cortisone and antimalarial therapy for the next 18 months. All medication has been discontinued during the past year and the patient is still well.

Results of Therapy

Thirty-six patients who had active skin lesions were observed while taking atabrine and chloroquine from a minimum of three months to as long as 30 months. An attempt was made to increase the dose of each drug to tolerance or maximal clinical improvement in each case, and to use the drugs synergistically if the results of therapy with one chemical were unsatisfactory. The results of applying this method to a series of systemic cases have been described by one of us.[13] In general, the dosages required among the discoid patients were a maximum of 0.4 gm. of atabrine and 0.75 gm. of chloroquine diphosphate daily. Not only did the cutaneous lesion undergo involution, as expected, but in this series the systemic manifestations were also benefited.

Eighteen of the 36 patients had complete healing of their cutaneous lesions, and the other 18 had a great deal of improvement. Fourteen of the 22 patients with localized discoid disease had complete healing, compared to four of 14 patients with the generalized form, although the duration and type of therapy were comparable. Eight patients who had complete disappearance of their lesions continued to return to clinic for follow-up. Of these, six had cutaneous relapses during a period which varied from three weeks to seven months after discontinuing therapy.

Twenty patients who had rheumatoid arthritis with "discoid lupus" received antimalarial therapy and all were benefited. In 10 of these the arthritis completely disappeared while on medication (see case 2). Three patients who had had arthritis were observed after the discontinuance of therapy, and none of these had a relapse after treatment had been discontinued for as long as a year. Atabrine has been reported to be of benefit in pure rheumatoid arthritis.[14, 15]

Discussion

The clinical data presented above illustrate the frequency of the systemic changes in discoid lupus erythematosus. It has been pointed out by others that these changes occasionally occur, but the fact that they are as important and characteristic a part of the clinical picture as the cutaneous lesions has not hitherto been demonstrated. O'Leary's classification of these patients into localized and generalized discoid, subacute disseminated and acute disseminated types has only relative usefulness. As noted from the accompanying tables and case reports, many of the so-called localized forms show advanced systemic change, whereas many of the generalized discoid forms remain localized primarily to the skin. In general, it appears that there is more chance of systemic change with extension of the cutaneous lesions below the chin. The entire classification of lupus is arbitrary because of the frequency of transition forms. Table 2 summarizes the frequency of systemic changes in each group. If evidence of one significant systemic change, such as rheumatoid-like arthritis or rheumatoid deformity, Raynaud's phenomenon, pericarditis, pleuritis, etc., was found by history or physical examination, the patient was classified as having some systemic involvement. Sixteen of the "localized discoid" group (62%) had such changes. In the generalized discoid group, 93% showed these manifestations. If, in addition, such laboratory changes as leukopenia, elevated sedimentation rates and hyperglobulinemia were considered, there was evidence of systemic changes in 24 of 26 patients with localized discoid lupus, and in all 15 of the generalized discoid group. In other words, there was evidence by this study of systemic changes in 39 of the 41 cases, or 96%.

There are other laboratory evidences of the fact that so-called discoid lupus is not primarily a cutaneous disease. The alpha one, alpha two and gamma globulins rise serially, and the albumins fall in the transition between discoid and acute systemic lupus.[16] There is also a rising percentage of false-positive serologic tests for syphilis as one goes from one form to another.[17] One of the best studies of the degree of systemic change in discoid lupus is that by Huff, Taylor and Keys, who demonstrated plethysmographic change in the fingers of patients with chronic discoid lupus offering clear evidence that in this disease there is a circulatory dysfunction in areas remote from the site of visible lesions.[18]

Summary

Chronic discoid lupus erythematosus has been regarded as primarily a skin disease with rare systemic manifestations. In order to determine the truth of this statement we performed a complete history, physical examination and routine laboratory work on a series of 41 patients with chronic discoid lupus erythematosus. The patients were divided into two groups: the localized discoid form with skin lesions above the chin, and the general-

ized discoid form with cutaneous involvement on the face and elsewhere. Sixteen of the 26 patients (62%) of the localized discoid group had evidence at some time in the course of their illness of arthritis, fever, Raynaud's phenomenon, pleurisy or other systemic changes by history and physical examination alone. Fourteen of the 15 cases of generalized discoid disease had such changes. If, in addition, laboratory abnormalities such as leukopenia, elevated sedimentation rate, hyperglobulinemia or abnormal flocculation tests were considered, then 24 of the 26 with localized discoid disease and all 15 of the generalized discoid group showed such changes. Therefore, there was evidence of systemic involvement in 96% of this group of patients with chronic discoid lupus.

Three different modes of onset of discoid lupus were found. Thirty-three patients (72%) had cutaneous changes initially, followed, in 45% of this group, by rheumatoid-like arthritis. Seven patients had rheumatoid arthritis prior to the appearance of discoid lesions. One patient had a biologic false-positive serologic test prior to her skin lesions.

The classification of lupus erythematosus is an arbitrary one. There are many transitions between the types. Discoid lupus, from its inception, is a systemic disorder which is a variant of the more malignant acute disseminated form. The "benign"-appearing cutaneous lesion may be a herald of advanced systemic manifestations which may be present at the same time or at a later date, when the skin changes have healed. Therefore, all these patients should have a thorough general medical survey. The form of therapy instituted depends entirely upon the extent of the disease.

SUMMARIO IN INTERLINGUA

Chronic discoide lupus erythematose ha essite considerate como primarimente un morbo cutanee con rar manifestationes systemic. Pro determinar le validitate de iste conception, nos executava un complete studio historic, examine physic, e investigation laboratorial routinari in un serie de 41 patientes con chronic discoide lupus erythematose. Le patientes esseva separate in duo gruppos: le gruppo de casos a forma discoide localisate, con lesiones cutanee supra le mento, e le gruppo de casos a forma discoide generalisate, con affectiones cutanee in le facie e alterubi. Dece-sex (62 pro cento) del 26 patientes in le gruppo de casos a forma discoide localisate monstrava a un o altere tempore in le curso de lor morbo signos de arthritis, febre, phenomeno de Raynaud, pleuritis, o altere alterationes systemic constatate super le base de solmente le historia del morbo e le examine physic del patiente. Dece-quatro del 15 patientes in le gruppo de casos a forma discoide generalisate habeva etiam tal alterationes. Si, in plus, anormalitates laboratorial—leucopenia, sedimentation accelerate, hyperglobulinemia, resultatos non-normal in tests de flocculation, etc.—esseva prendite in consideration, alora 24 del 26 patientes in le gruppo de casos a forma discoide localisate e omne le 15 patientes in le gruppo de casos a forma discoide generalisate exhibiva alterationes del typos mentionate. Assi 96 pro cento del casos in iste gruppo de patientes con chronic lupus discoide monstrava un involvimento systemic.

Esseva constatate tres differente modos de declaration de lupus discoide. Trenta-tres patientes (72 pro cento) habeva initialmente alterationes cutanee que esseva sequite, in 45 pro cento del casos in iste gruppo, per arthritis rheumatoide. Septe

patientes habeva arthritis rheumatoide ante le manifestation de lesiones discoide. Un patiente habeva un reaction biologic falsemente positive ante le declaration de su lesiones cutanee.

Le classification de lupus erythematose es arbitrari. Il existe multe formas transitional inter le typos. Lupus discoide, ab le tempore de su inception, es un disordine systemic que representa un variante del plus maligne acute forma disseminate. Le lesiones cutanee con lor apparentia "benigne" pote esser le heraldo de plus avantiate manifestationes systemic. Istos pote esser presente simultaneemente o illos pote disveloppar se plus tarde quando le alterationes cutanee es curate. Per consequente, omne tal patientes deberea esser subjicite a un exacte examine medical general. Le forma del therapia a seliger depende integremente del grado de extension del morbo.

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EVALUATION OF THREE DIAGNOSTIC PROCEDURES FOR SYSTEMIC LUPUS ERYTHEMATOSUS *

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DEMONSTRATION of the cellular aggregation which constitutes the lupus erythematosus (LE) phenomenon in heparinized bone marrow [1] was the basis of the first in a series of specific diagnostic procedures in systemic lupus erythematosus (SLE).[2] When this phenomenon was also demonstrated in heparinized [3] and in clotted [4] peripheral blood of patients suffering from this disease, such preparations were also used in laboratory diagnosis. Finally, the reproduction in vitro of the LE phenomenon by adding LE plasma or serum to cells of normal bone marrow [5, 6] added another in this series of tests.

Thus, the three types of diagnostic procedures used have in common their dependence upon the demonstration of the LE phenomenon in the patient's bone marrow, in his peripheral blood or after appropriate incubation of his serum or plasma with normal bone marrow cells. Each procedure has its own adherents, whose preference usually is based on familiarity with a specific technic. The purpose of the present study was to compare these three technics from the several aspects of sensitivity, accuracy, facility, availability of controls, and the occurrence of false-positive or false-negative results.

METHOD AND MATERIAL

Since 1949 the special hematology laboratory of the Cleveland Clinic has performed over 7,000 LE tests, using as the routine procedure the LE plasma to dog marrow technic.[7] Prior to this the patient's own bone marrow (Hargraves' procedure) had been perfectly satisfactory except for minor disadvantages which will be dealt with later. In a similar manner, those LE tests which utilized the peripheral blood methods were and still are acceptable. In general, in patients with classic severe systemic lupus erythematosus the LE tests were positive by any technic. The differences between the LE tests were more apparent with the recognition of the atypical varieties of systemic lupus erythematosus, or of the so-called "lupus diathesis." [8] These patients usually had a low grade illness, often were more well than sick, and were suspected of the tendency toward systemic lupus erythematosus because of rheumatoid arthritis and one or more of the fol-

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lowing manifestations: anemia, leukopenia, polyserositis, splenomegaly, false-positive serologic tests for syphilis, epilepsy, purpura, Raynaud's phenomenon, renal disease or photosensitivity.[9]

Many of the patients with the lupus diathesis did not have strongly positive LE tests and showed variations among the three methods. It was in this group of patients with an atypical and therefore controversial illness, rather than in those with the classic type of systemic lupus erythematosus, that the comparative differences in the LE tests were noted. A series of 79 such patients were tested by all three technics in a period between 1952 and 1954. Follow-up studies were obtained on those in whom any or all of the LE tests were positive, and in a proportionate number of patients in whom all of the tests were negative.

In order to evaluate the acceptance of the various LE tests, a questionnaire was sent out to a small group of hematologists, selected because of geographic location as well as because of a special interest in the LE phenomenon. They were asked to give their experience with the various LE tests and to express a frank evaluation as to their worth.

Results and Comment

Thirty-three of the 79 patients with atypical systemic lupus erythematosus had positive results on one or more of the three LE tests (table 1). There were no distinguishing features between the clinical manifestations of these patients and those of the patients who had negative tests. It will be noted that there is a variation in sensitivity among the tests. The clotted peripheral blood LE test was positive in 30 of these patients, the patient's own marrow LE test was positive in 24, and the plasma-dog marrow LE test was positive in 19. It should be emphasized here that these results are in patients with low grade illness, and are at variance with those when the three procedures are compared in patients with severe systemic lupus erythematosus. In the latter group the peripheral blood and the plasma-dog LE tests are frequently positive while the patient's own marrow procedure, due perhaps to the not infrequent hypoplastic marrow associated with the disease, may be negative.[10]

The follow-up studies in this small group of patients revealed no deaths, and many were asymptomatic. By contrast, of 63 patients with severe systemic lupus erythematosus seen during the same period of time, 15 are dead. Thus, these studies would appear to permit some relaxation in the fear associated with a weak positive LE test. One might more readily conclude that, as is the case so often in clinical medicine, the outlook for each individual patient is based on the sum total of the entire clinical and laboratory evaluation, rather than on a reliance upon any single laboratory procedure.

The variations in the sensitivity of the three LE tests are perhaps due to the use of heparin in the patient's own marrow and the plasma-marrow

procedures, and to its absence in the clotted blood technic. One of the main difficulties with the plasma-dog marrow LE test is the tendency to overheparinize the dog marrow before it is sent to the hematology laboratory. Furthermore, the deliberate addition of excessive heparin to any LE procedure will result almost invariably in a negative test. The exact mode of action of the heparin against the LE phenomenon is in doubt. Patients

TABLE 1

Comparison of Three LE Tests in Patients with Atypical Systemic Lupus Erythematosus

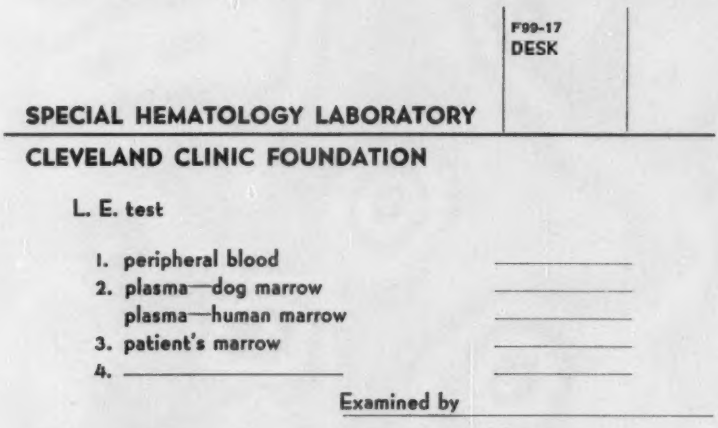
Case	Date	Own Marrow	Own Blood	Plasma-Dog Marrow	Working Diagnoses	Outcome—1955
M. H.	10–31–52	+	+	0	R.A. gangrene	Living, symptomatic
M. P.	10–31–52	?	+	0	R.A.	Living
F. G.	11–18–52	0	+	0	R.A., diabetes	Living
B. K.	12–2–52	+	+	0	R.A., diabetes	Living and well
A. J.	12–2–52	+	+	0	R.A.	Same diagnosis
M. S.	1–29–53	0	+	+	Hemolytic anemia, rheumatoid arthritis	Asymptomatic
T. W.	3–24–53	+	+	0	R.A.	Asymptomatic
R. B.	6–12–53	+	0	?	Apresoline reactor	Living
I. S.	9–29–53	+	++	+	LE, nephrosis	Living
G. W.	12–2–53	+	+	+	SLE	Living
M. S.	10–5–53	+	+	+	SLE	LE in remission
M. B.	10–27–53	+	?	0	LE diathesis	Living and well
F. T.	11–6–53	+	+	+	LE, nephrosis	Living
V. W.	11–12–53	+	+	+	Apresoline reactor	Living and well
A. C.	11–17–53	+	+	+	Apresoline reactor	Living and well
V. M.	11–24–53	0	+	0	LE diathesis	R.A.
A. H.	11–25–53	+	+	?	LE diathesis	Living and well
F. G.	12–7–53	+	+	+	SLE	Remission
M. D.	1–18–54	+	+	0	R.A.	R.A.
M. K.	1–19–54	0	?	+	LE	LE in remission
A. M.	1–19–54	0	+	0	Apresoline reactor	Living
H. Z.	2–12–54	+	+	+	LE	LE in remission
P. G.	3–12–54	0	+++	++	Apresoline reactor	Living
L. M.	3–17–54	+	+	+	LE	LE
V. S.	3–17–54	+	+	+	LE	Remission
E. P.	3–22–54	+	+	+	LE	Remission
M. D.	3–30–54	+	+	+	LE	Remission
I. M.	4–6–54	+	+	0	LE	Remission
E. H.	4–13–54	+	+	+	LE	Remission
S. S.	7–2–54	0	+	0	LE	Remission
E. S.	8–31–54	+	+	+	LE	Remission
B. S.	9–27–54	0	+	+	LE diathesis	Remission
F. R.	12–31–54	+	+	+	LE, nephrosis	Same diagnosis

with systemic lupus erythematosus who have been heparinized do no better or worse than those who have not been, and there is no in vivo effect on the LE test. This suggests that the action of heparin is not directly upon the LE factor, but may be an in vitro effect on the phagocytic phenomenon. In other words, instead of destroying the LE factor it may simply be a block between the phagocytizing cells and the nucleoprotein.

Besides sensitivity, other points of difference were noted among the three LE tests. Thus, while false-negative LE tests were more likely to occur

with the two procedures requiring heparin, "false-positive" clotted peripheral blood LE tests were more common, particularly in the Apresoline reactors. The procedure for the peripheral blood LE test can easily be done in an office, but the interpretation of the same test requires an expert, due to the paucity of cells. The patient's own bone marrow and the plasma-marrow technics are hardly office procedures, but their interpretation is easier to learn, due to the more obvious demonstration of the LE phenomenon in marrow preparations.

The plasma-marrow procedure has four distinct advantages over the other two methods. First, since it is an in vitro procedure, it is possible to compare the bone marrow cells being tested for their viability, by using as a control plasma known to contain the LE factor, as well as a control using


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L. E. test

1. peripheral blood _____
2. plasma—dog marrow _____
   plasma—human marrow _____
3. patient's marrow _____
4. _____ _____

Examined by _____

17 L. E. TEST

FIG. 1. "Battery" of LE tests as listed on laboratory report. The entire group of LE tests may be done if the routine (plasma-dog marrow) LE test is equivocal.

normal plasma. Second, LE plasma can be sent long distances for testing against preparations obtained where bone marrow is more readily available. Third, the same LE plasma sample can be used repeatedly with different bone marrow preparations. This has the advantage of disturbing the patient but once, and permits doubtful results to be resolved by repetitive testing. Finally, the in vitro procedure is the only one of the three LE tests useful as a research method.[11]

In recognition of the advantages of each of the LE tests, an "LE battery" has been found useful (figure 1). This is employed when the clinician is convinced that the patient has lupus erythematosus, and the first LE test is indefinite.

When complete laboratory facilities are not available, these studies sug-

TABLE 2

Evaluation of LE Tests by 20 Hematologists

Hematologist	Reliability			Tests Used				Number of LE Tests per Year			False-Negatives	False-Positive Tests				Interpretation by Hematologists
				Patient's Own Marrow	Own Blood		Serum									
	90–95%	50–90%	Not Rel.		Cltd.	Hep.		150+	50–150	0–50		Penicillin	Apresoline	Chloral	Other	
1	+			0	0	+	0	+			Frequent	0	0	0	0	Highly specific
2	+			0	+	0	0		+		5	0	0	0	0	A valuable test
3	+			+	+	0	0			+	0	0	0	0	0	
4	+			0	+	0	0		+		0	0	2*	0	0	*I don't consider these "false."
5	+			+	+	0	0		+		Rare	0	0	0	0	
6	+			0	+	0	0	+			?	0	2	0	0	
7			+	+	+	+	0			+	Yes	0	0	0	**	**Must be repeated many times.
8	+			0	+	0	0			35	2	0	0	0	0	
9		+		+	+	+	0		+		0	0	0	0	1	
10	+			+	+	0	0			+	2	0	0	0	0	
11		+		+	+	+	0	+			Yes***	0	0	0	0	***40% false negatives.
12	+			0	+	0	0	+			0	0	0	0	0	
13		+		+	+	+	0		+		7	2				
14	+			+	+	+				+	?	0	0	0	0	Very reliable test.
15	"When positive"			0	+	+	0		+		0		#		1±	#Acute glom. nephritis—autopsy
16	+			+	+	+	0	+			?	1?				
17	+			+	+	+	+	+			Yes	0	6##			##"Not really" false positive.
18	+				+					+	0	0	0	0	0	
19	+			+	+	+	+		+		Yes	0	###	0	0	###More specific than the Wassermann test.
20	+				+			+			Yes	0	1	0	0	

gest that a practical and accurate evaluation can be started as an office procedure by combining the peripheral blood and the plasma-marrow technics. Thus, 10 c.c. of blood are obtained from the patient and allowed to clot, and and the serum is put aside. The peripheral blood LE test is done on the cellular material. If this procedure is positive or equivocal, the serum is still available for testing against bone marrow material. It may be held in a refrigerator for days or weeks until marrow is available, or it may be sent to centers where marrow LE tests are done.

Twenty hematologists gave opinions on their use of LE tests (table 2). Each section of the country was represented by two or more authorities. Thirteen stated that their laboratories performed over 50 LE tests per year. Conley, of The Johns Hopkins University,[12] stated that more than 1,000 LE tests were performed in his Hematology Research Laboratory in 1954. Using a variety of technics to demonstrate the LE phenomenon, he found the LE tests to be more reliable than the Wassermann test as far as specificity is concerned. He felt that the reported lack of specificity of the LE test was most often due to the failure to "adhere to the rigid criteria in identifying LE cells."

Only one hematologist stated that LE tests were not reliable. Fifteen found the tests to be 90 to 95% reliable, in the general sense of dependability. Of interest was the preponderance of false-negative over false-positive reactions. Thus, many felt that the LE tests were occasionally negative when the clinical evaluation of the patient indicated active systemic lupus erythematosus. On the other hand, true false-positive LE tests, as reported by this group of hematologists, were rarities. Only one experienced a positive LE test in penicillin sensitivity, and another found one test to be "questionable." Apresoline reactors were not so rare. More than 11 such cases were found to have positive LE tests, but three of these authorities did not really regard these as "false-positive" LE tests because the entire clinical syndrome so closely resembled systemic lupus erythematosus. One stated that "this phenomenon may be important in providing a clue to the pathogenesis of systemic lupus erythematosus."

Summary and Conclusion

Three methods for inducing the LE phenomenon were compared from the various aspects of sensitivity, accuracy, facility, availability of controls, and the occurrence of false-positive and false-negative results.

All three procedures were found to be positive in classic examples of severe systemic lupus erythematosus, except for occasional false-negative results in the patient's own bone marrow procedure. (This was due presumably to the occasional hypoplastic marrows associated with the disease.) The differences between the three LE tests were more apparent in patients with low grade illness, or the so-called "lupus diathesis." In this group

the peripheral blood LE test (clotted) was the most sensitive, the patient's own marrow LE test the next, and the plasma-dog bone marrow LE test the least sensitive. Of 33 such patients followed up to three years, all were living, suggesting that a weak positive LE test by itself is not necessarily of serious prognostic importance.

A survey was made of 20 hematologists, selected by geographic location as well as because of a special interest in the LE phenomenon. In general, these authorities found the LE tests to be specific. False-negative LE tests were not infrequent in the face of typical systemic lupus erythematosus, but false-positive LE tests, such as in penicillin sensitivity, were rare. Positive LE tests in Apresoline reactors were not considered to be "false-positive," due to the close clinical resemblance with systemic lupus erythematosus.

The clotted peripheral blood LE test and the plasma-bone marrow LE test were found to have special advantages. A combination of both is suggested as a practical office procedure.

SUMMARIO IN INTERLINGUA

Tres methodos pro inducer le phenomeno del aggregation cellular characteristic de lupus erythematose (LE) esseva comparate ab le puncto de vista de sensibilitate, exactitude, facilitate, disponibilitate de controlos, e occurrentia de resultatos pseudo-positive e pseudo-negative.

Omne le tres methodos se provava de efficacia positive in casos classic de sever LE systemic, excepte que alicun resultatos pseudo-negative occurreva in le methodo utilisante un specimen de heparinisate medulla ossee del patiente mesme. [Isto esseva probabilemente occasionate per le medulla hypoplastic que es a vices associate con LE.] Le differentias inter le tres tests pro LE esseva plus apparente in patientes con basse grados del morbo, i.e. in casos del si-appellate "diathese a lupus." In iste gruppo le test a (coagulate) sanguine peripheric esseva le plus sensibile; le test a medulla ossee ab le patiente sequeva; e le test a plasma addite a medulla ossee canin esseva le minus sensibile. Trenta-tres tal patientes, qui esseva observate durante tres annos, superviveva sin exception. Isto indica que un positive test a LE non es per se de necessarimente grave signification prognostic.

Un questionario esseva submittite a 20 hematologos, seligite secundo lor location geographic e etiam a causa de lor interesses special. In general iste autoritates trovava que le tests a LE es specific. Pseudo-negative tests a LE non esseva infrequente in casos de typic systemic lupus erythematose; sed pseudo-positive tests a LE, del genera occurrente con sensibilitate a penicillina, non esseva reportate. Positive tests a LE in reactores a apresolina non esseva considerate como "pseudo-positive" proque le integre syndrome es si simile a systemic lupus erythematose. Le test a coagulate sanguine peripheric e le test a plasma addite a medulla ossee habeva avantages special. Un combination del duo es recommendate como procedimento practic al sala de consulta.

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ESSENTIAL PULMONARY HYPERTENSION: A REPORT OF CLINICAL-PHYSIOLOGIC STUDIES IN THREE PATIENTS, WITH DEATH FOLLOWING CATHETERIZATION OF THE HEART *

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ESSENTIAL pulmonary hypertension is a condition in which the elevation in pulmonary artery pressure results from an increase in the vascular resistance in the lung. The exact cause of the pulmonary vascular changes is not definitely established, but the possibility exists that in some instances repeated asymptomatic pulmonary embolizations can produce the vascular changes found in this disease.[3, 44] Other terms for this condition are pulmonary vascular obstruction syndrome or primary pulmonary hypertension.[3, 12, 15, 16, 17, 38]

Prior to the introduction of cardiac catheterization, primary pulmonary hypertension was considered rare. In 1931 McCallum reported one case in 12,000 autopsies at the Johns Hopkins Hospital.[26] Killingsworth described one case in 2,707 autopsies at Children's Memorial Hospital in Chicago.[25] Since cardiac catheterization is now a common procedure, the diagnosis of primary pulmonary hypertension is made more frequently.

The present paper is a report dealing with clinical and physiologic studies on three patients, and with postmortem studies in two of them. Two of the patients were under 15 years of age; the third was 33 years old. All three patients died after cardiac catheterization had been completed.

CASE REPORTS

Case 1. A 14 year old schoolboy was admitted to the University Hospital on March 3, 1955, because of fainting spells of one year's duration and congestive heart failure of three months' duration.

Present Illness: Three attacks of syncope lasting a few minutes had occurred during the last year; all had taken place after physical exertion. There was no associated tongue biting or incontinence. Following the third episode the patient complained of nausea and shortness of breath and was placed on bed-rest. There were moderate edema of the legs, questionable swelling of the abdomen and puffiness about the eyes. He was hospitalized for a few days, but no specific medications were given.

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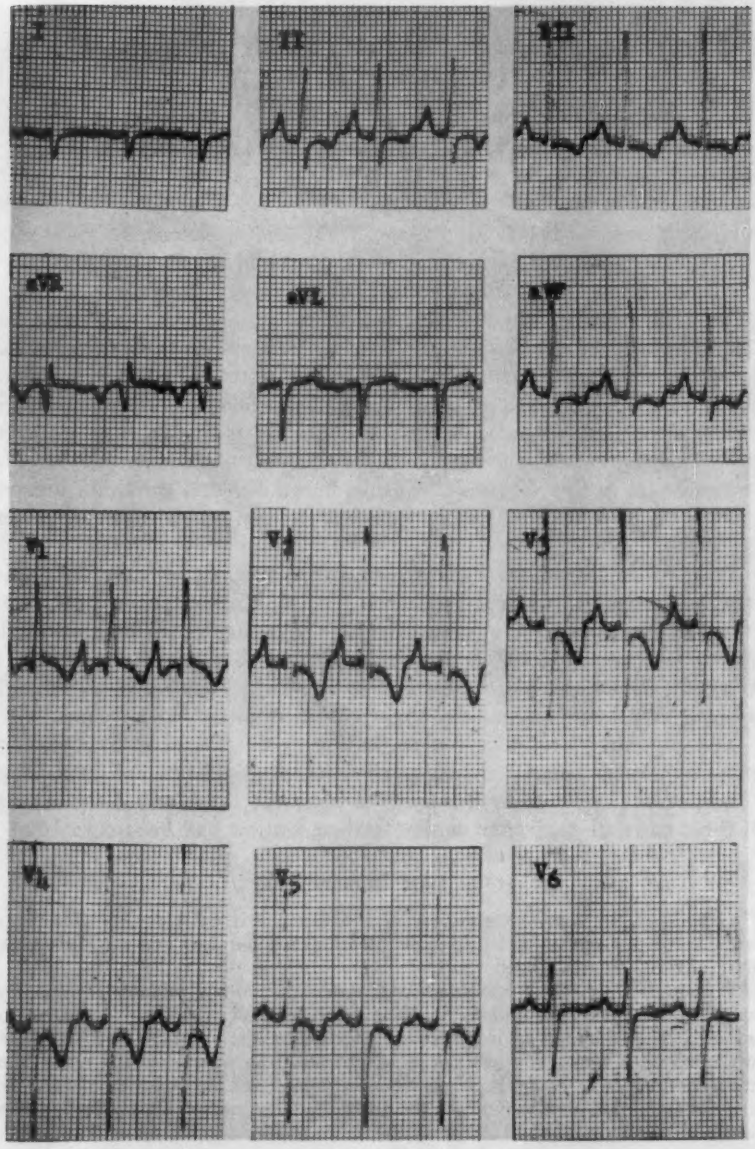


FIG. 1. *Case 1.* (February 22, 1955.) There are pointed P waves in Leads I and II, and in the right chest leads. Lead V_1 shows a prominent R deflection, but no S wave, and in V_2 there is only a diminutive S wave. The intrinsicoid deflection is delayed in these leads. The other chest leads present an S deflection which increases toward the left side of the precordium. ST segments are depressed in all the chest leads and are followed by inverted T waves.

One month before the present admission there was a recurrence of nausea and vomiting, accompanied by shortness of breath. He was admitted to a hospital and placed in an oxygen tent for about 18 hours. He recovered and had no residual complaints.

Physical Examination: Inspection revealed a well proportioned but small white boy who appeared two or three years younger than his stated age. He seemed comfortable at rest and there was no cyanosis or clubbing, no edema or ascites.

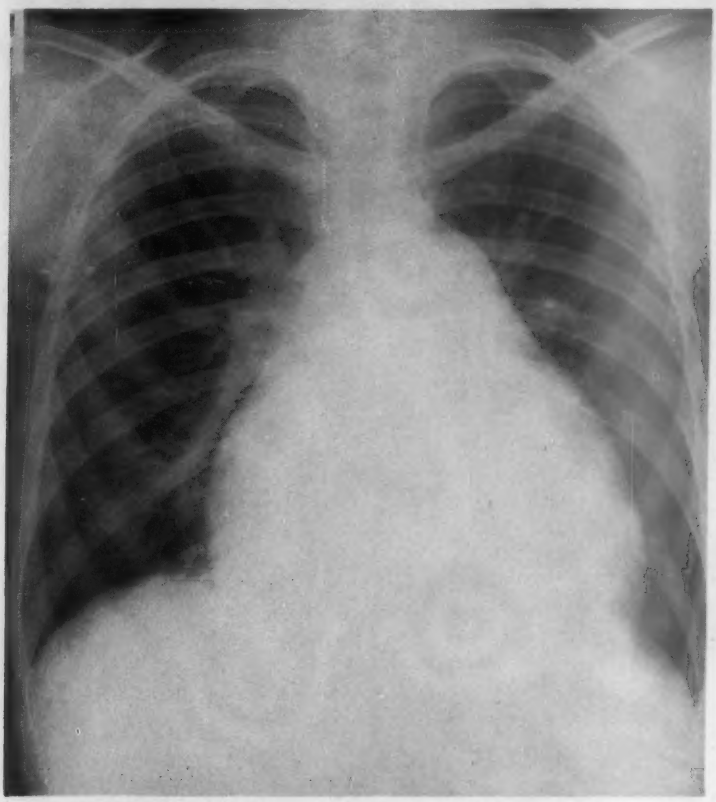


FIG. 2 A. *Case 1.* A-P view shows a generally enlarged heart, with prominent pulmonary artery segment and enlarged hilar vascular shadows. Intrapulmonary vascular markings are normal.

The neck veins were slightly distended. The systemic blood pressure was 102/95 mm. of Hg in the right arm, 105/85 mm. of Hg in the left arm. The lungs were clear to percussion and auscultation. The chest showed a moderate pigeon-breast deformity. On inspection there was marked diffuse precordial activity. The point of maximal impulse was felt over a wide area extending laterally to the left anterior axillary line at the fifth interspace. No thrill was felt. In the pulmonic area there was a very pronounced diastolic shock. On auscultation a Grade III systolic murmur was audible over the entire precordium, with its maximal intensity in the mitral

area. The murmur was transmitted to the left axilla. In a well localized area over the apex of the heart there was a low-pitched diastolic murmur. A diastolic gallop was also heard over most of the precordium. The pulmonic second sound was markedly accentuated. The liver was not tender but was palpable five fingerbreadths below the right costal margin. There were good arterial pulsations. No cyanosis or clubbing was present.

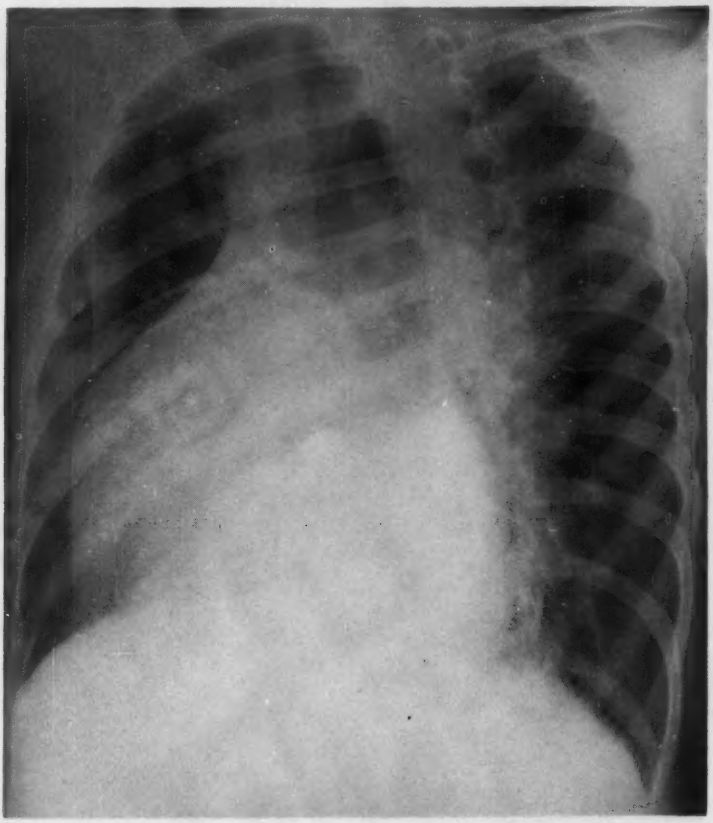


FIG. 2 B. *Case 1.* In the left anterior oblique view the left ventricle overlaps the spine due to displacement by a large R.V.

Laboratory Studies: Urinalysis: negative, except for a very few traces of albumin. Hemoglobin, 15.5 gm.%; red blood cells, 5 million; white blood cells, 5,250, with lymphocytosis; erythrocyte sedimentation rate (Wintrobe), 13 mm./hr.; C-reactive protein and antistreptolysin titer, negative. The electrocardiogram was consistent with right axis deviation (Axis-QRS + 105°), right atrial and right ventricular hypertrophy and myocardial damage (figure 1). Fluoroscopy and chest x-rays in the A-P view showed a globular, enlarged heart (figures 2a to 2c). The pulmonary artery segment was convex, the hilar vessels were prominent, and the vascularity of

the peripheral lung fields was normal. In the oblique views the right ventricle appeared to be enlarged. Clinical impression was rheumatic heart disease, probably mitral stenosis and insufficiency with chronic congestive failure. The possibility of a coexisting atrial septal defect with pulmonary hypertension was also considered. Because of the uncertain diagnosis, catheterization was performed on March 21, 1955.

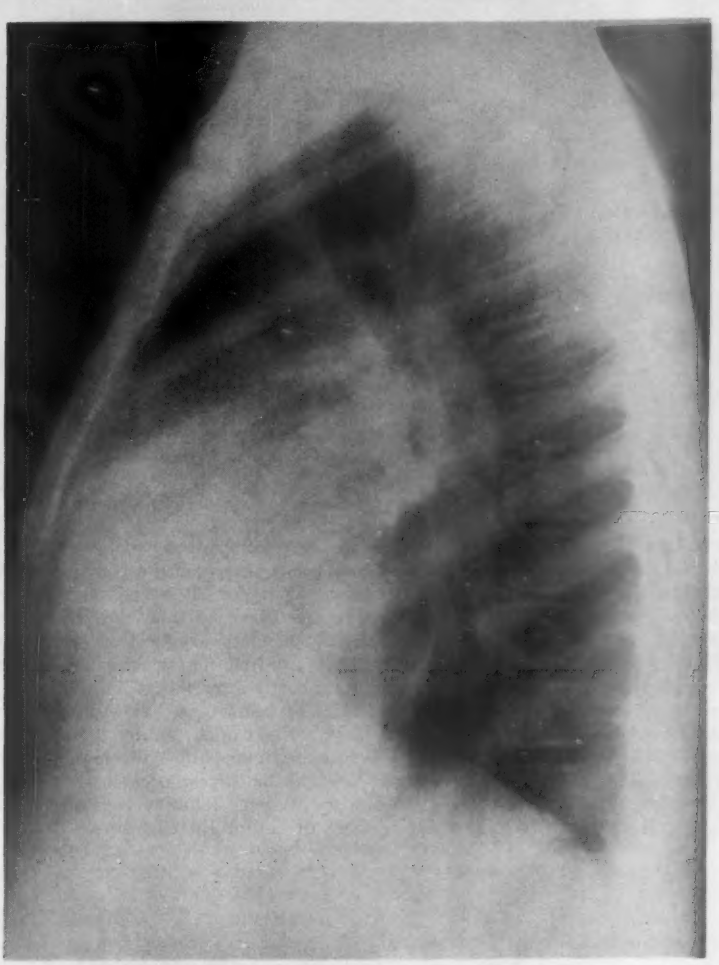


FIG. 2C. *Case 1.* In the left lateral view the retrocardiac space is obliterated by the enlarged right ventricle.

The superior vena cava, right auricle, right ventricle, main pulmonary artery and right pulmonary artery were intubated without incident. Blood samples were taken from these locations and the pressures recorded (figure 3). Data obtained during cardiac catheterization are illustrated in table 1. Five minutes after ca-

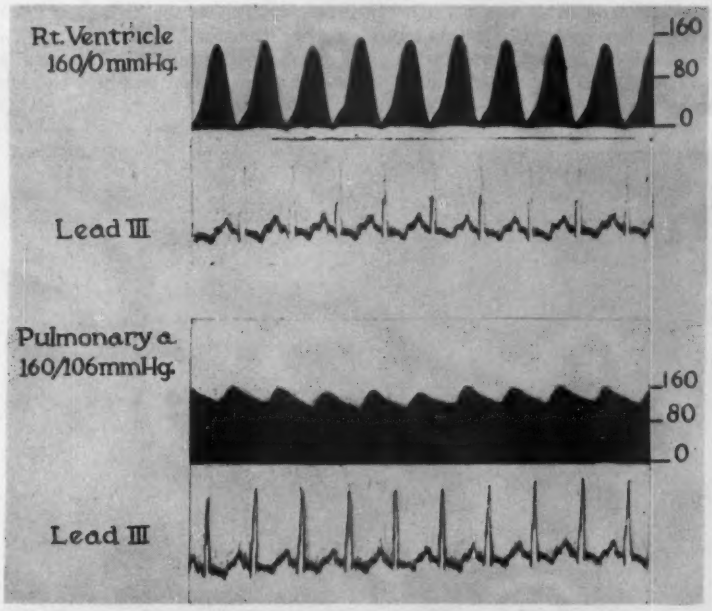


FIG. 3. *Case 1.* Marked pulmonary hypertension and elevated right ventricular pressure.

theterization, as the incision was sutured, the child complained of nausea. He said that he felt "choking about the heart"; a few seconds later he had a convulsion, which lasted about 30 seconds. He became conscious again for 20 seconds and responded normally. However, another epileptiform seizure occurred, and the child died 15 minutes later. The electrocardiogram showed changes varying from sinus tachycardia to complete A-V heart block (figure 4). First, the auricles and ventricles beat regularly at the rate of 125 per minute. Shortly after this, the ventricular rate slowed down to 50 per minute, and two auricular beats were followed by one ventricular complex, resembling a 2:1 heart block. Eight minutes after the second convulsion the electrocardiogram showed ventricular standstill with maintenance of auricular beats. Two minutes later complete cardiac arrest occurred.

The pertinent features obtained at autopsy were as follows: Heart weight was 410 gm. There was tremendous enlargement of both right chambers. Both atrial

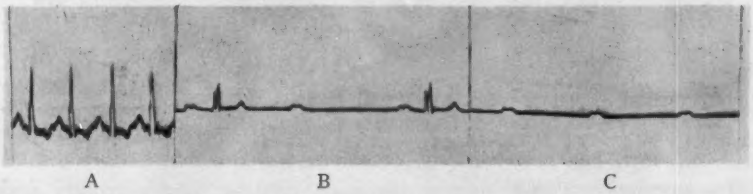


FIG. 4. *Case 1.* A. Tracing obtained during cardiac catheterization shows normal sinus rhythm. B. Following catheterization, idioventricular rhythm developed. C. Ventricular arrest with maintenance of auricular beats.

and ventricular walls were hypertrophied. The tricuspid valve measured 12.5 cm. in diameter. The wall of the right ventricle measured 1.0 cm., the pulmonary artery was very dilated, and the pulmonic valve measured 7 cm. in diameter. There was a slight degree of arteriosclerosis in the walls of this vessel. The right pulmonary artery measured 4.5 cm., the left, 3.5 cm. in diameter. No defects in the atrial or ventricular septum were found. The left atrium and ventricle were of normal size.

The lungs were red-pink in color. There was some congestion in the posterior zones of both lower lobes.

Histologic Examination: The most important alterations were found in the arteries and in the perivascular zones (figures 5a to 5c). The arterioles were affected by a process of intimal proliferation which in some instances led to their complete occlusion. The media was generally thickened, and the adventitial tissue was rich in small congested vessels, with an accumulation of chronic inflammatory cells of nonspecific type. The septa showed chronic congestion with engorged vessels and subsequent thickening without apparent inflammation. There was a marked degree of arteriosclerosis in the larger branches of the pulmonary artery, with accumulation of macrophages of foamy aspect and mucoid degeneration of the media.

TABLE 1

Data Obtained during Right Heart Catheterization

Patients	Name	Sex	Age, yrs.	Date	Surface Area	O_2 Capacity vol. %	O_2 Contents (vol. %)					Pressures mm. Hg		
							S.V.C.	R.A.	R.V.	M.P.A.	R.P.A.	R.A.	R.V.	P.A.
1	N. L.	M	14	3-24-55	1.20	21.6	6.0	5.0	4.8	4.7	5.0	28/20	160/0	160/106
2	A. S.	F	7	5-1-52	1.00	21.3	10.2	8.6	7.0	7.1	7.7	26/4	162/43/0	167/129
3	H. B.	M	33	12-29-54	—	—	—	—	—	—	—	19/9	—	150/80

Case 2. A seven year old girl was admitted to the University Hospital for the second time on April 30, 1952, because of numerous syncopal episodes, occurring since the age of two years and characterized by unconsciousness, palpitation of the heart and cyanosis.

Present Illness: The patient had previously had several syncopal episodes, not associated with tongue biting or incontinence. The last episode had occurred three weeks prior to the present admission. During this attack the patient complained of pains in the precordial region, and became unconscious and apneic. Palpitation of the heart and slight cyanosis were observed by the physician. Following this episode, chest pain, fatigability and general weakness were present. There had been no previous history of rheumatic fever or edema.

Physical Examination: The seven year old girl appeared to be small for her age. Some shortness of breath was noticeable. No cyanosis, clubbing or edema was present. There was slight engorgement of the neck veins, with little pulsation. The left chest showed a moderate bulge over the precordial region. Systemic blood pressure was 112/90 mm. of Hg in the right arm, 140/100 mm. of Hg in the left leg. The pulse rate was 120 per minute. The point of maximal impulse was forceful but rather diffuse; it was felt over a wide area to the left of the midclavicular line. No thrill was present. On auscultation a soft, blowing systolic murmur to the left of the sternum was heard, with its maximal intensity in the second intercostal space. No definite diastolic murmur was audible. The second pulmonic sound was markedly accentuated. Percussion and auscultation of the lung fields were normal. The

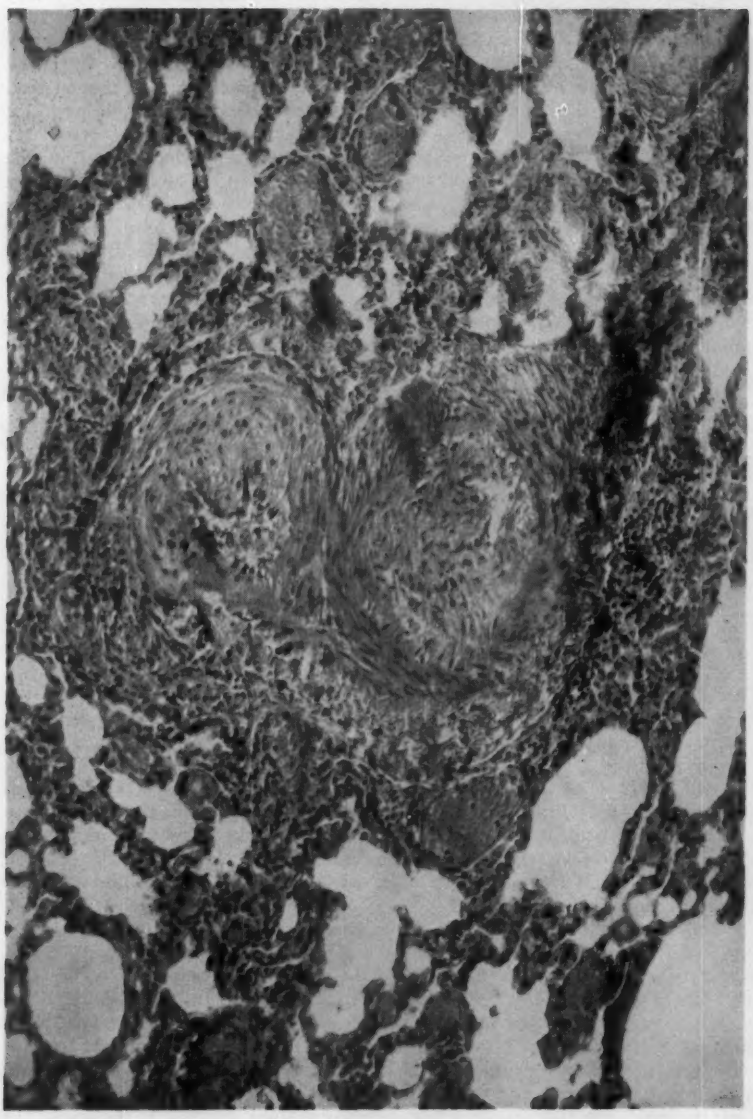


FIG. 5A. *Case 1.* Pulmonary arterioles are almost occluded by intimal proliferation and mild chronic perivascular inflammatory changes.



FIG. 5 B. *Case 1.* Secondary branch of the pulmonary artery, with marked arteriosclerotic changes.

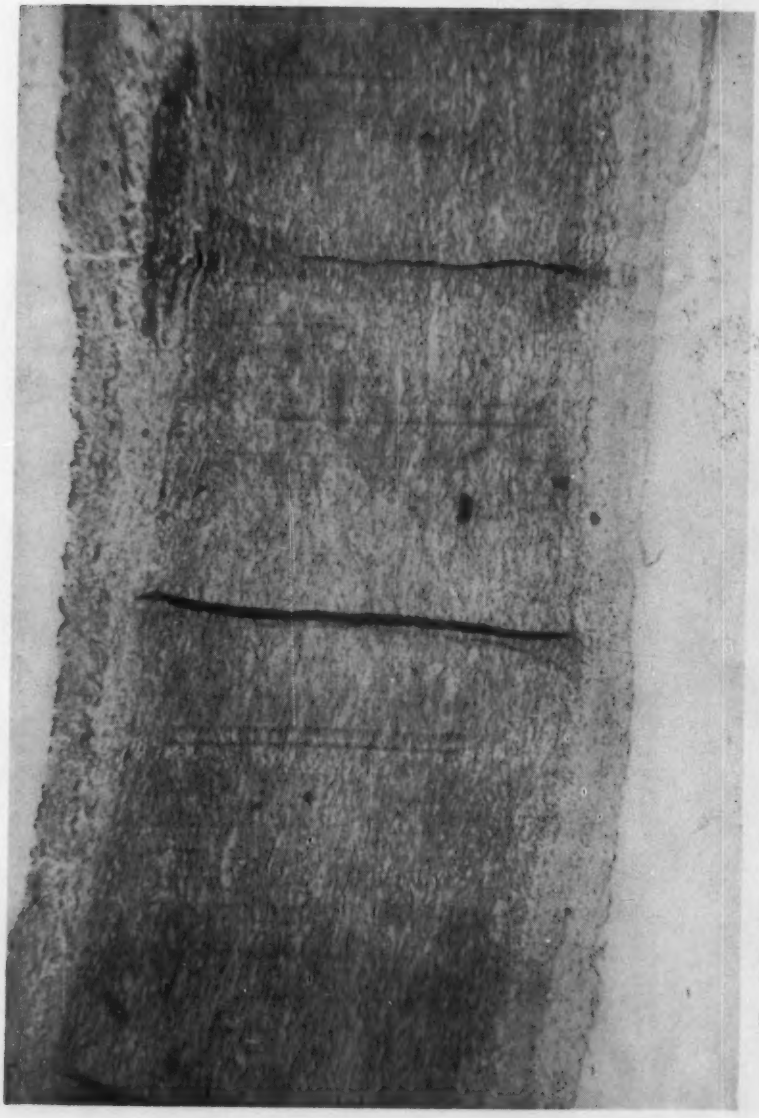


FIG. 5C. *Case 1.* Main branch of the pulmonary artery, showing slight intimal thickening and marked degenerative changes in the media.

liver was enlarged and palpable two fingerbreadths below the right costal margin.

Laboratory Studies: Urinalysis, negative. Hemoglobin, 14.5 gm.%; red blood cells, 4.7 million; white blood cells, 9,100, with moderate lymphocytosis.

The electrocardiogram was consistent with right axis deviation (Axis-QRS +125°), right ventricular hypertrophy and myocardial damage (figure 6). Fluoroscopy showed enlargement of the heart to the left and to the right. The pulmonary artery segment was convex. Hilar vessels appeared prominent, but the vascularity of the peripheral lung fields was decreased. In the oblique positions the right ventricle appeared particularly enlarged; no displacement of the barium-filled esophagus was discernible.

Clinical impression was pulmonary hypertension or congenital heart disease with a left-to-right shunt. Catheterization was performed on May 1, 1952.

Intubation of the chambers of the right heart and the pulmonary artery was carried out without incident. Pressures in the right ventricle and the pulmonary artery are shown in figure 7. The data obtained on cardiac catheterization are summarized in table 1. As the incision was sutured the patient felt sick and vomited. The heart rate slowed suddenly from 140 to 30 beats per minute, and the child became unconscious. The electrocardiogram first showed normal sinus rhythm, then complete A-V block. This was followed by auricular standstill, with maintenance of ventricular beats of 30 beats per minute. Twenty-five minutes after the syncopal attack, complete cardiac arrest had occurred. Autopsy permission was not obtained.

Case 3. A 33 year old male was admitted to the University Hospital because of "cold and fever."

The patient was said to have been in fair health until December 20, 1954, at which time he noted a gradual onset of dyspnea which progressed to complete incapacitation. Another complaint was "deep hurting" across the anterior chest, radiating to both arms and shoulders.

On admission the patient was found to be acutely ill. Tachypnea, orthopnea and cyanosis were present. Blood pressure was unobtainable in either arm. The femoral pulses were palpable and equal on both sides. Pulse rate was 105 per minute. The respiratory rate was 30 per minute. The lung fields were clear to percussion and auscultation. A Grade III systolic murmur was heard over the apex and a somewhat similar systolic murmur over the pulmonary area. In addition, there was a diastolic murmur with its maximum intensity over the second or third left intercostal space. The liver and spleen were not enlarged.

Fluoroscopy revealed generalized cardiac enlargement. This is also apparent in the x-ray (figure 8). The pulmonary artery segment was prominent and pulsated vigorously. The hilar markings were increased but hilar dance was absent.

The electrocardiogram showed moderate right axis deviation and was indicative of marked right ventricular hypertrophy.

Clinical impression was congenital heart disease (ventricular septal defect), with acute insufficiency of the pulmonic valve.

Cardiac catheterization was performed eight hours after admission. The systolic pressure in the right ventricle and in the pulmonary artery as measured during catheterization was 150 mm. Hg. Ten minutes following the procedure the patient developed ventricular tachycardia and died.

Autopsy Findings: The heart weight was 700 gm. The outstanding finding was enlargement of both right chambers, showing a thickening of the muscular wall of the atrium and the ventricles. The left side of the heart appeared normal. Atherosclerosis of the pulmonary artery and its branches was present, and the pulmonary vessels were dilated.

Histologic examination revealed intimal and medial thickening of the pulmonary arterioles, with almost complete occlusion of these vessels.

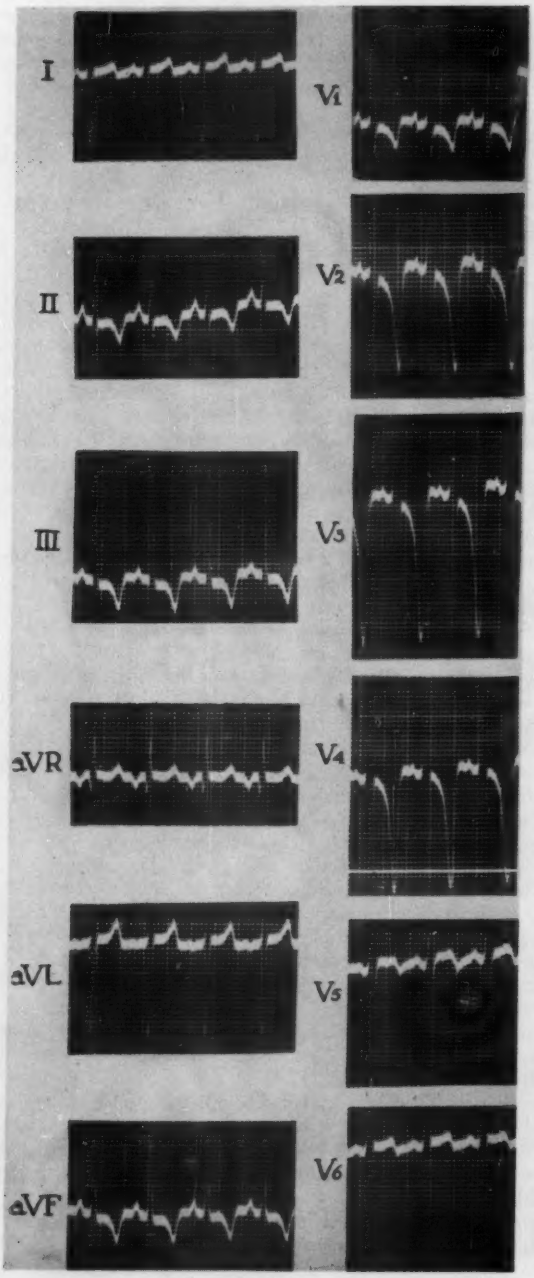


FIG. 6.

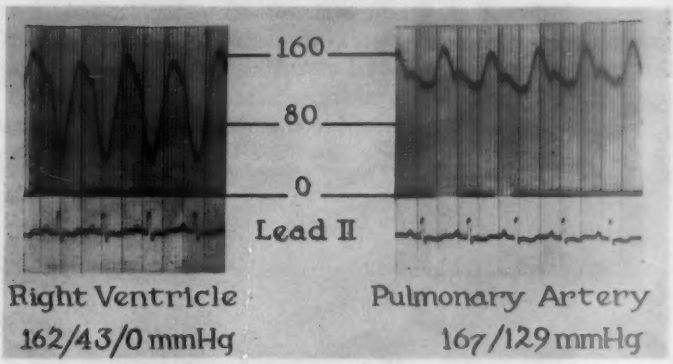


FIG. 7. *Case 2.* Shows marked increased pressures in the pulmonary artery and right ventricle.

COMMENTS

The histories of the three patients described in this report show certain common features. Two of them (cases 1 and 2), both children, suffered from effort syncope. In case 1 the periods of unconsciousness lasted for several minutes; in case 2 they were accompanied by palpitation of the heart, cyanosis, and pain over the precordial region. In the adult patient (case 3) no syncopal attacks are known. All three patients had a history of shortness of breath, which was particularly severe in case 3.

Effort syncope as a prominent symptom of primary pulmonary hypertension has been described by a series of authors.[1, 7, 17, 18, 25, 26, 28] Some observers place the incidence of effort syncope in this condition at 20%.[16] Dressler reports that these syncopal attacks are often preceded by premonitory symptoms of lightheadedness, dizziness, feeling of epigastric fullness, choking or a tight feeling about the heart.[18] According to this author the duration of unconsciousness varies from a few seconds to several minutes. In most patients the attacks are accompanied by tachycardia, with increased respiratory rate. However, Dressler reported one patient in whom a heart rate of 64 per minute was observed immediately following the attack.[18]

Several theories have been advanced to explain the nature of these syncopal attacks. Some observers feel that they are related to acute right heart failure.[17] The possibility exists that they are due to sudden impairment of the coronary circulation resulting from a rise in right ventricular end-diastolic pressure.[10] Others believe that the attacks may be related to a vasomotor reflex, originating in the walls of the pulmonary artery, with

FIG. 6. *Case 2.* (January 18, 1952.) Tall and pointed P waves are seen in Lead II. Lead V_1 shows a prominent R deflection. The S waves in the chest leads increase toward the left side of the precordium. The ST segments are depressed in Leads III and AVF and in the right chest leads through V_4. Elevation of the ST segments is noted in AVL and over the left precordial area. The T waves in V_1 through V_4 are deeply inverted and show signs of marked myocardial damage.

the vagus serving as the afferent arch of this reflex.[18] This hypothesis is based on the experimental work of Schwiegk, de Burgh Daly and Aviado.[2, 10, 85] Schwiegk severed all vascular connections to one lung, leaving the pulmonary branches of the vagus intact. When pulmonary artery pressure was raised by injection of blood through a cannula inserted into

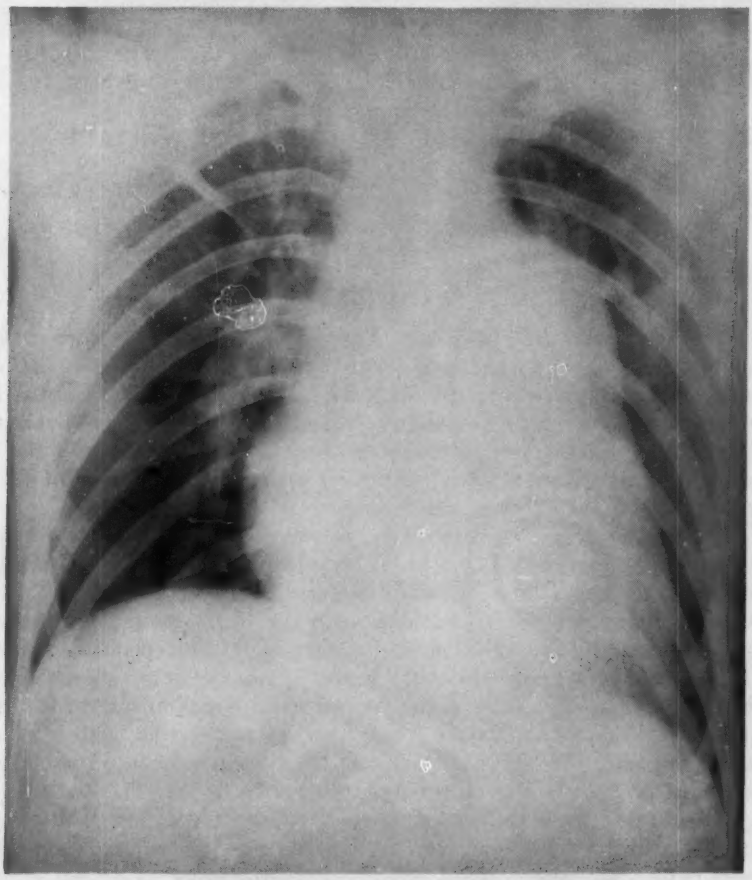


FIG. 8. *Case 3.* Shows generalized cardiac enlargement.

the distal portion of this vessel, bradycardia and a fall in systemic blood pressure were recorded. The fall in peripheral arterial pressure was proportional to the elevation in pulmonary artery pressure. These hemodynamic effects were absent after cutting of the pulmonary branches of the vagus. The results were interpreted as suggesting the presence of a reflex, with pressor receptors located in the walls of the pulmonary artery.

Daly, using preparations in which pulmonary and systemic circulations could be perfused separately, also found that an increase in pulmonary flow gave rise to a slight but definite fall in systemic arterial pressure. The heart rate either rose or fell during these experiments. These effects did not appear after section of both cervical vagosympathetic nerves. Aviado concluded from extensive experimental studies that there is a reflex system arising from stretch receptors located in the bifurcation of the pulmonary artery which gives rise to bradycardia and a fall in systemic blood pressure.

A history of shortness of breath was obtained in all three patients of this series. In two of them (cases 1 and 3) it was present at rest. The association of dyspnea with primary pulmonary hypertension has been described by a series of authors.[1, 4, 7, 8, 9, 10, 14, 15, 16, 17, 18, 19, 20, 22, 25, 26, 32, 33, 36] The mechanism of this dyspnea may also be related to the presence of sensory receptors in the pulmonary vascular bed. Aviado found that on raising the pressure in the perfused pulmonary artery and ligating the pulmonary veins, tachypnea occurred, which he believed to be the result of a pulmonary reflex, with the receptors located at or near the origin of the pulmonary artery and in the pulmonary veins.[2] An acceleration of respiration was also observed by Daly in some of his preparations. Increased respiratory frequency has been observed to follow the introduction of multiple emboli into the pulmonary circulation.[6] It is also known that reflex tachypnea can result from the introduction of veratridine into the pulmonary veins. Aviado concluded that the drug stimulates the same receptors that respond to elevated pressure in the pulmonary veins. This suggests that some of the effects on respiratory rate observed under experimental conditions bear a close resemblance to the Bezold-Jarisch reflex. Dyspnea similar to that produced by veratridine can also be elicited by pulmonary congestion and by experimental pulmonary edema.[11, 31]

Physical examination revealed that all patients of this series had a systolic murmur. In two (cases 1 and 3) a diastolic murmur was also heard. In cases 1 and 3 the maximal intensity of the systolic murmur was at the apex; in case 2 it was in the second left intercostal space. The diastolic murmurs were of lower intensity, with maximal intensity over the apex or in the second left intercostal space. Both systolic and diastolic murmurs had been previously observed in essential pulmonary hypertension by Soothill,[36] Dresdale [17] and Stone and Powles.[38] The systolic murmur may be the result of a relative tricuspid insufficiency or of a dilation of the pulmonary artery. The diastolic murmur may be produced by relative insufficiency of the pulmonary valve. The presence of these murmurs is sometimes responsible for diagnostic errors, since murmurs of this type and location are not infrequently encountered in patients suffering from congenital and rheumatic heart disease. For example, in one patient of this series (case 1) a diagnosis of congenital or rheumatic heart disease was made on the basis of clinical findings alone. A constant finding in all pa-

tients described in this report and in the literature is the accentuation of the second pulmonic sound.

The electrocardiograms in the patients of this series showed right axis deviation and right ventricular hypertrophy (figures 1 and 6). During catheterization no special irregularities in the electrocardiogram were observed. However, during the attacks the electrocardiogram showed marked alterations. Case 1 first developed sinus tachycardia, followed by 2:1 or 3:1 A-V block, with a ventricular rate of 125 per minute. Following this, a 2:1 block with ventricular rate of 50 per minute was observed. Finally, ventricular standstill occurred, with an auricular rate of 50 per minute (figure 4). In case 2 a sudden decline in ventricular rate from 140 to 30 beats per minute, with a complete cessation of auricular complexes, was recorded. Case 3 developed ventricular fibrillation.

The findings on fluoroscopy obtained on the patients in this series are similar to those described by others in essential pulmonary hypertension. The hilar markings are increased but the peripheral pulmonary vascular markings are diminished. Right ventricle and the pulmonary artery segment are prominent. The relatively clear peripheral lung fields distinguish this condition from congenital heart disease with a large left-to-right shunt.

Data obtained on cardiac catheterization are summarized in table 1. The most significant finding was marked increase in pulmonary artery pressure. Since the condition of the patient made it impossible to collect expired air and arterial blood samples, cardiac output and pulmonary vascular resistance could not be calculated. However, with mean pulmonary artery pressure exceeding 150 mm. Hg, the pulmonary vascular resistance must have been significantly elevated.

The microscopic findings recorded on two patients (cases 1 and 3) furnish the explanation for the increased pulmonary vascular resistance. In both cases there was medial and intimal thickening of the pulmonary arterioles. The proliferation in the walls of the arterioles was particularly conspicuous, leading to almost complete occlusion of the lumina. The stem of the pulmonary artery showed arteriosclerotic changes. These findings are in accord with those obtained by other workers.[7, 8, 17, 19, 20, 25, 26, 28]

The deaths of the patients of this series may be due to a series of related factors. If results obtained in the experimental animal by Schwiegk, de Burgh Daly, Aviado and Schweitzer are applicable to man, death may have occurred as a result of stimulation of receptors in the wall of the pulmonary arteries and veins. A diminution in heart rate observed in two patients of this series could then be interpreted as due to reflex vagal stimulation. However, the presence of these reflexes has never been conclusively demonstrated in man. Another explanation for the sudden death is the occurrence of acute right heart failure. Howarth and Lowe demonstrated a decrease in pulse pressure in the right ventricle with a rise in right ventricular end-diastolic pressure, suggesting acute failure of the right ventricle.[23] Related to this

is the further possibility that inability to increase cardiac output leads to relative coronary insufficiency and to cerebral ischemia. Syncopal attacks similar to those occurring in essential pulmonary hypertension are known to occur in conditions in which cardiac output is limited by the presence of aortic stenosis. In essential pulmonary hypertension the impediment to flow is located at the level of the pulmonary arterioles. In these conditions the demand of the heart muscle for increased oxygen supply cannot be satisfied, because of this limitation in cardiac output. The ensuing decline in peripheral blood flow then leads to cerebral ischemia. It is of interest that syncopal attacks in congenital heart disease with pulmonary hypertension are rare. Apparently under these conditions the increase in right-to-left shunt is sufficient to prevent cardiac and cerebral ischemia.

This report again stresses the fact that the life of patients with essential pulmonary hypertension is continually menaced. Death has occurred even after such usually harmless diagnostic procedures as the determination of the circulation time with Decholin, and also after the administration of barbiturate anesthesia for sympathectomy.[15, 24] One death following catheterization has been previously reported by Cutler.[15] Great care should therefore be taken in carrying out any diagnostic procedure on patients with essential pulmonary hypertension. In over 900 patients on whom catheterization of the heart has been performed within the last three and one-half years at the Medical College of Alabama, the three cases described represent the only fatalities encountered.

SUMMARIO IN INTERLINGUA

Le presente reporto es concernite con constatationes clinic, physiologic, e pathologic in tres patientes de hypertension pulmonar essential. Duo esseva juveniles, le tertie un adulto. Le constatationes clinic consisteva de attaccos syncopic, palpitation, e dyspnea. Le constatationes physic revelava le presentia de un murmure cardiac. Le electrocardiogramma monstrava hypertrophia dextero-ventricular e deviation dextrorse del axe. Studios physiologic revelava un marcate augmento del pression pulmono-arterial. Su valor median excedeva 150 mm Hg. Le constatationes pathologic microscopic esseva le spissification medial e intimal del arteriolos pulmonar. Nos discute le causa del morte in iste patientes e sublinea le facto que le vita de personas con hypertension pulmonar essential es constantemente menaciate.

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STUDIES OF CHOLESTEROL SYNTHESIS IN MAN USING CARBON^{14} LABELED ACETATE *

By GEORGE V. LEROY, M.D., *Chicago, Illinois*

CHOLESTEROL is an important constituent of the body. The total amount in a 70 kg. man is 0.3% of the wet weight, or 210 gm. The content of individual tissues ranges from 0.12% in red cells to 4.5% in the adrenal gland.[1] Since practically no cholesterol is oxidized to carbon dioxide to yield energy, it is of interest to investigate the function of this relatively abundant solid alcohol. It is known that certain bile acids and their salts, which are important for the digestion of fat, are derived from cholesterol. The plasma cholesterol is believed to play a key rôle in the transport of neutral fat by means of the lipoprotein fractions of the blood. Cholesterol has been found to be a precursor of several steroid hormones, including some produced by the adrenal gland and some by the gonads. The relationship between cholesterol and atherosclerosis is, of course, of great contemporary interest. Finally, there is reason to believe that cholesterol has an influence on some immunologic reactions, and that it may participate in the detoxification of certain classes of poisons.

Our interest in cholesterol is related to studies of steroid hormones and to the metabolic fate of acetate. The material presented will be restricted to a consideration of what we have learned about the synthesis of cholesterol from acetate in man. The majority of the work reported has been carried out at the Argonne Cancer Research Hospital of the University of Chicago.

Bloch and Rittenberg [2] and their colleagues have demonstrated that the reaction **acetate → cholesterol** is the only one involved in the biosynthesis of cholesterol in mammals. Gould and his group [3] have shown by studies of hepatectomized dogs that the liver is the principal site for synthesis of the free cholesterol which later appears in the plasma, and is a precursor of plasma ester cholesterol. Cholesterol is synthesized from acetate in other organs, and we have demonstrated abundant extrahepatic production in the adrenals, ovaries and placenta of human subjects.[4]

The average diet contains about 0.5 gm. of cholesterol, and this can be increased to nearly 7 gm. per day by the addition of high-cholesterol foods, such as eggs. Studies with tritium-labeled cholesterol have shown [5, 6] that 20 to 50% of the tracer dose is absorbed from the gastrointestinal tract. Most of the cholesterol in the body, then, consists of a mixture of exogenous or dietary cholesterol, and endogenous cholesterol. In the case of the plasma the endogenous cholesterol is of hepatic origin. It appears that cholesterols

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of various origins are indistinguishable unless a tracer study is performed.[6]

The extent of the daily turnover of cholesterol is still a subject of dispute which involves, among other factors, the philosophy and the mathematics of a tracer experiment. Using heavy water and following its incorporation into cholesterol, London and Rittenberg[7] calculated a turnover time of approximately 12 days. In our laboratory we have made estimates of turnover in several patients using either carbon ^{14}-acetate or labeled cholesterol.

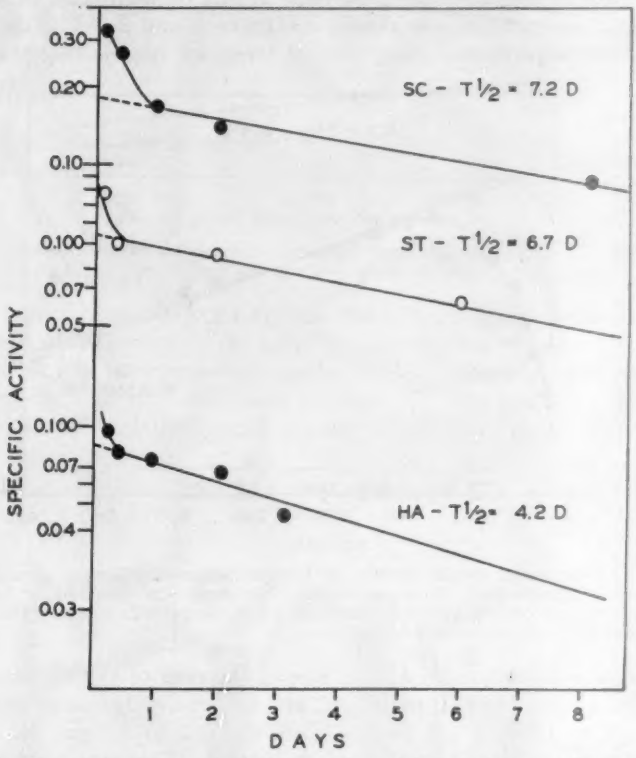


FIG. 1. Curves showing the decline in specific activity of cholesterol-C^{14} following an oral dose of 100 μc C^{14}-acetate. The upper two curves are for euthyroid subjects; the turnover times are 10 and 9.6 days, respectively.

Our values range from eight to 12 days for euthyroid subjects, and this agrees with the preliminary report of Kurland, Lucas and Freedberg.[8] Their studies also show that labeled cholesterol is excreted in the feces at the rate of about 3% per day. The group at the Sloan-Kettering Laboratory, led by Hellmann and Gallagher, interpret their data in a different manner, and report that cholesterol turnover is characterized by three rate components: a rapid, an intermediate and a slow one, with half-turnover

times of about eight hours, three days and 20 days, respectively. Our group, which includes Gould, believes that the period between the second and the tenth to the fourteenth days after the tracer dose can be used to estimate turnover with reasonable confidence. We have found that there is a very rapid interchange between the free cholesterol of the liver and that of the plasma, so that the liver-plasma system can be considered as one large, rapidly exchanging compartment. It seems proper to include the cholesterol passing through the enterohepatic circuit in this compartment. Examples of our data on turnover are shown in figures 1 and 2. The data were derived from experiments using several forms of labeled cholesterol. If

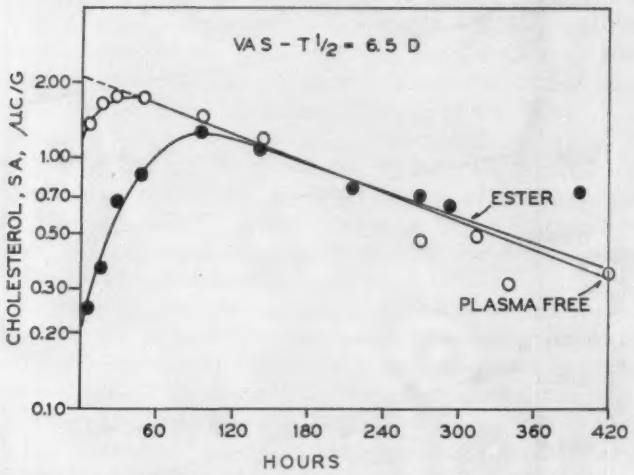


FIG. 2. Decrease of specific activity of tritium-cholesterol following intravenous administration. Approximately 30 μc of tritium cholesterol was dissolved in 1.0 ml. of propylene glycol, and this in turn dispersed in 25 ml. of the patient's plasma. The turnover time for this euthyroid subject is 9.4 days.

one accepts our interpretations, the size of the pool of rapidly exchanging cholesterol ranges from 20 to 30 gm., and has an average turnover time of from eight to 12 days. It follows, then, that 2.0 to 3.0 gm. per day are involved in the metabolic turnover of cholesterol. This represents to us the amount of cholesterol that must enter the liver-blood system each day to replace physiologic losses. We would say, then, that the body utilizes from 2 to 3 gm. per day, of which the smaller fraction may come from the diet. On the basis of this estimate, the major source of new cholesterol in man is believed to be hepatic synthesis, which appears to contribute, on the average, 2 or more gm. per day of newly formed cholesterol.

There is good reason to believe that the synthesis of cholesterol in the liver is under homeostatic control, the nature of which is now being studied. As a result of our interest in the phenomena relating to the regulation of

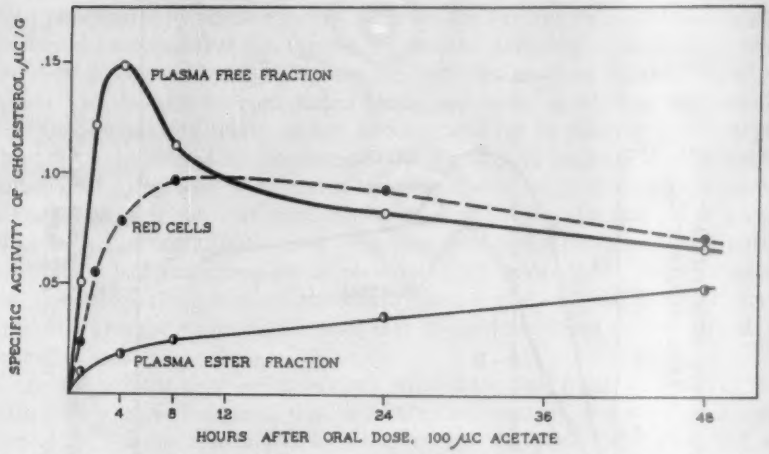


FIG. 3. Composite specific activity-time curve for blood cholesterol after an oral dose of 100 μc C^{14}-acetate. These are average values for 8 euthyroid subjects.

production, we have developed a procedure for estimating the relative rate of synthesis of cholesterol by the liver.[10] When a tracer dose of 100–200 μc of acetate is given intravenously or orally, the specific activity of plasma free cholesterol rises rapidly, as shown in figure 3. We can infer from the studies in dogs [8] that the specific activity of liver free cholesterol has in-

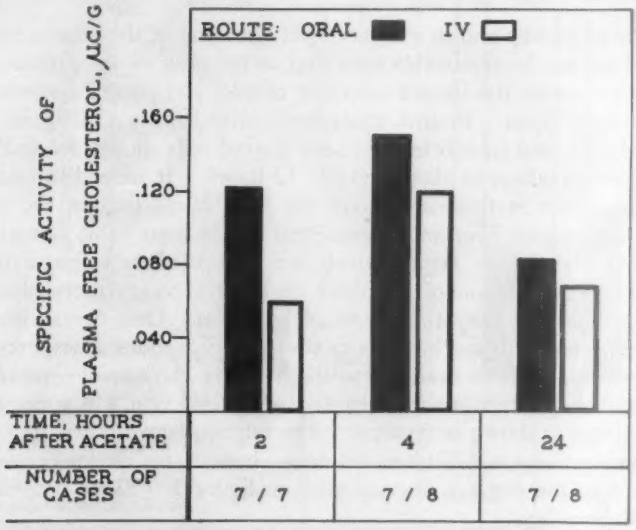


FIG. 4. Influence of route of administration of C^{14}-acetate on the specific activity of plasma free cholesterol at 2, 4 and 24 hours after a tracer dose of 100 μc.

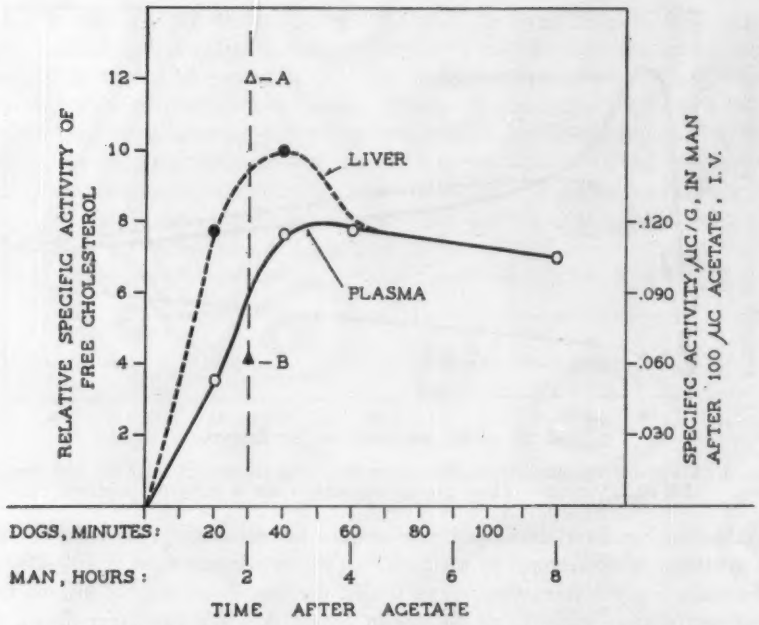


FIG. 5. Relationship between specific activity of liver free cholesterol and plasma free cholesterol following C^{14}-acetate. It is assumed that the situation in man is comparable to that observed in dogs.

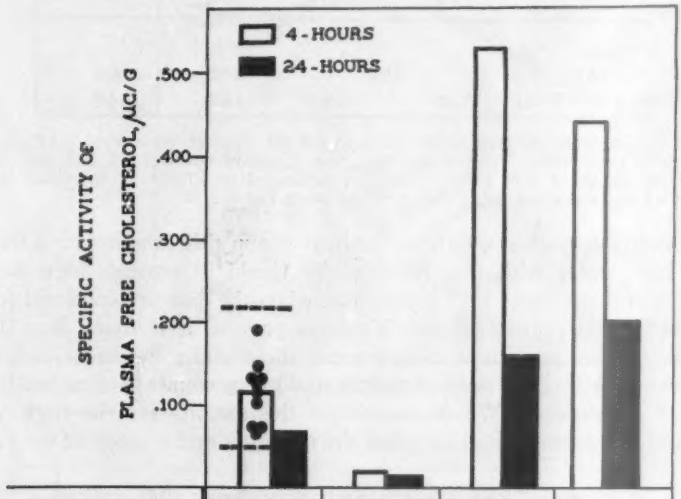
creased more rapidly and to a higher level than that of the plasma free fraction; and we can be reasonably sure that at the peak of the plasma specific activity-time curve, the specific activities of liver and plasma cholesterol are approximately equal. Plasma cholesterol interchanges rapidly with that of the red cells, and equilibrium between the red cells cholesterol and plasma free cholesterol occurs at about eight to 12 hours. It seemed to us that the significant points in this curve were the peak value, that is, the point of equilibrium between liver and plasma, and the 24 hour value at which time the exponential decline begins which we have used to estimate turnover time. The equilibration of the ester cholesterol occurs more slowly and may be completed at any time from 24 hours on. Oral doses yield somewhat larger values for specific activity than do intravenous doses, presumably because more acetate is available to the liver for cholesterol synthesis than is the case when the tracer is given in a peripheral vein. A comparison of the two routes is shown in figure 4. The relation between hepatic synthesis and plasma activity is difficult to determine in man, for obvious reasons, but the results in the dog are demonstrated in figure 5. These data are from Gould's laboratory.

The results of our studies in normal individuals are shown by the bar graphs in figure 6. We think that the range of normal values for the four

hour peak varies by about a factor of 2 from the average value of 0.120 μc/gm. It should be noted that the figures for specific activities scale directly with the dose of tracer used. When we studied nine cases of myxedema, all of whom had definite hypercholesterolemia, we found a striking decrease in the rate of synthesis, which cannot be accounted for by dilution in the larger amount of cholesterol in the plasma. In a group of patients with so-called collagen diseases who were under treatment with large doses of cortisone, remarkably high rates of synthesis were found. In a survey of a group of cases with generalized cancer who were not under treatment with cortisone, some had responses which we considered normal, but approximately one patient in three had an abnormally rapid rate of synthesis. In such cases the average value of the peak was about four times that observed in normals.

At the present time we cannot say what these data mean in terms of the actual amount of cholesterol that is synthesized per day, but we find it convenient to assume that a fourfold increase in the peak value observed at four hours is equivalent to a fourfold increase in the amount synthesized, and probably also in the amount turned over per day, and vice versa.

It is possible to calculate the fraction of the dose of acetate that is utilized



DIAGNOSIS	EUTHYROID	MYXEDEMA	CORTISONE	CANCER
NUMBER OF CASES	8	9	5	5
AVERAGE VALUE FOR 4 HR. SAMPLE, μC/G	0.117	0.019	0.535	0.447

FIG. 6. Bar graph showing average values for specific activity of plasma free cholesterol 4 and 24 hours after intravenous C^{14}-acetate in four groups of subjects.

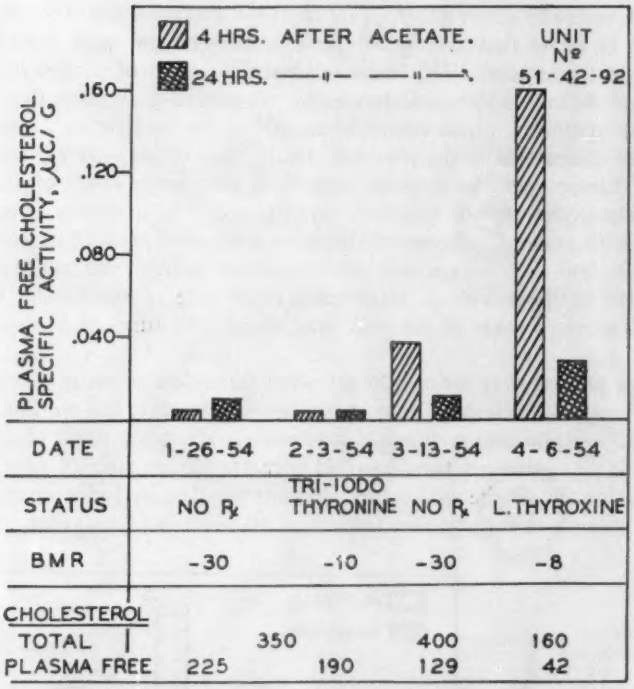


FIG. 7. Influence of replacement therapy on the rate of cholesterol synthesis in a patient with myxedema. Tri-iodo-thyronine was given in doses of 70, 105 and 175 μg. respectively, on the 3 days prior to the test performed on 2/3/54. L-thyroxine in daily doses of 0.1 mg. was given for 12 days prior to the test of 4/6/54.

for cholesterol synthesis. In our normal group this amounts to 1.04%, a value comparable with that obtained by Gould in normal dogs, namely, 1.1%. In the patients with myxedema, when the data are corrected for the increased blood cholesterol that is always present, it is found that 0.23% is used. In our patients with cancer and those under treatment with cortisone, nearly 4% of the dose of acetate could be accounted for as newly synthesized cholesterol. We do not know the reasons for the high values observed in the latter situations, but the matter is under study at the present time.

We have studied our patients with myxedema after various forms of therapy with the following results:[11] When tri-iodo-thyronine is given for one to two days the basal metabolic rate increases rapidly, while the plasma free cholesterol lags behind. A typical example is shown in figure 7. As a matter of fact, it may be changed very little in this short period of time. It is of interest that the rate of synthesis does not increase in a manner parallel to the basal metabolic rate, a result that is shown in the figure.

When the more slowly acting thyroxine is used there appears to be a close parallel between the increase in the basal metabolic rate and the decrease of plasma cholesterol (figure 8). Under these circumstances the rate of synthesis, as measured by the acetate method, shows a change to normal type of response at the time the euthyroid state is attained. These findings suggest the existence of a homeostatic mechanism for regulation of hepatic synthesis of cholesterol, which is dependent upon the level of the plasma free cholesterol. We estimate that the cholesterols of plasma and liver interchange rapidly, at a rate which approximates 0.8 gm. per hour. It seems to us that this could be the basis for homeostatic control, but further study is required before a definite statement can be made.

We have also tested euthyroid subjects prior to the induction of hypothyroidism by radioiodine. After myxedema is evident the normal response following acetate is no longer seen, and the typical low rate of synthesis of myxedema is observed. Our studies of patients with hyperthyroidism have not been conclusive, and are, in fact, quite variable. We had expected that the patient with active Graves's disease would have an increased rate

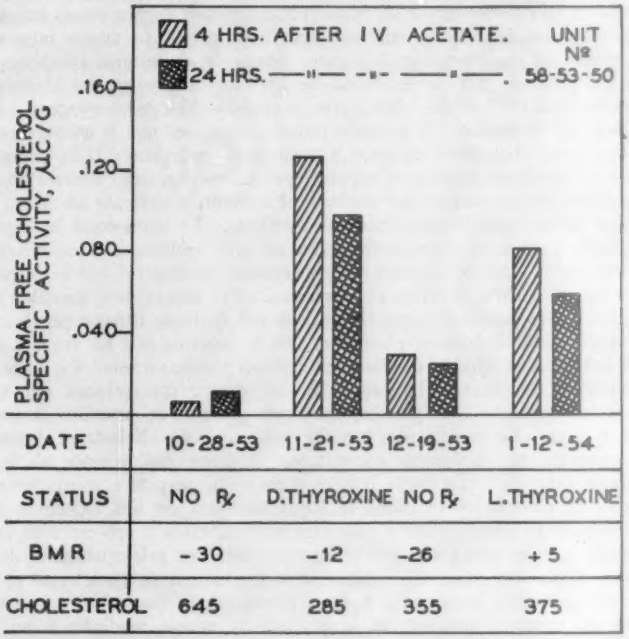


FIG. 8. Influence of replacement therapy on the rate of cholesterol synthesis in myxedema. The second test (11/21/53) was performed after the patient had received 1.0 mg. per day of d-thyroxine. At that time the drug was stopped and clinical relapse was evident at time of third test, 12/19/53. Remission was produced by l-thyroxine in doses of 0.1 mg. per day.

of synthesis and a more rapid turnover rate. We have found the turnover rate to be increased, but the pattern of synthesis is not clear.

When acetate is given intravenously, we have found that approximately 1% is converted to cholesterol. Most of this synthesis appears to be completed rapidly, probably within the first two to four hours. During the same period of time approximately one third of the radiocarbon appears in expired air as carbon dioxide. Over a period of 24 hours approximately 60% of the radiocarbon is excreted as $C^{14}O_2$, and approximately 2% of the radiocarbon appears in the urine, principally as bicarbonate and urea. The balance of the acetate is widely distributed in many compounds, including fatty acids, amino acids, nucleic acid units and the like. These studies illustrate in a very comprehensive manner a practical technic for the study of many aspects of cholesterol metabolism in man. The dose of radiocarbon is well within the permissible limit, so that repeated tests can be performed.

SUMMARIO IN INTERLINGUA

Cholesterol es de interesse pro le clinico a causa de su distribution extense in le corpore, su function como precursor de certe hormones steroide, su rolo in le disveloppamento de atherosclerosis, e su relation al intensitate de reactiones immunologic. Le presente discurso describe le studios nunc in progresso in nostre laboratorio in re le biosynthese de cholesterol in humanos. Omne le cholesterol synthetisate in le corpore es un producto del condensation de acetato. Un parte del cholesterol del sanguine es derivate ab le dieta. Iste parte se appella cholesterol exogene. Le resto es synthetisate per le hepate. Il ha nulle ration a supponer que le corpore pote facer un distinction inter cholesterol exogene e cholesterol endogene. Il es probabile que le velocitate del synthese hepatic es regulate per un mechanismo homeostatic. In le caso de humanos, le proportion del cholesterol sanguinee derivate ab le un o ab le altere del duo fontes non es cognoscite con certitude. Le cholesterol in hepate, sanguine, e lympha pote esser considerate como un unic systema con un characteristic velocitate metabolic. Altere organos e histos contine cholesterol que es in parte synthetisate in sito e in parte derivate ab le plasma. Per administrar amontas traciator de acetato a C^{14} il es possibile sequer le prorata del synthese hepatic per le curso del activitate specific del cholesterol plasmatic. In le practica nos ha trovate opportun determinar le activitate specific de libere cholesterol plasmatic inter 4 e 24 horas post le administration del dosage traciator. Si on desira estimationes del velocitate metabolic e del extension del systema, specimens pote esser prendite durante plure septimanas o plus. Le novemente formate moleculas de cholesterol (representate pro le investigator per moleculas etiquettate) se move rapidemente ab le cellulas hepatic a in le sanguine. De facto, il pare occurrer un rapide e constante excambio de moleculas de cholesterol in omne le locos studiate per nos. Quando doses de acetato etiquettate es administrate a subjectos normal, circa 1 pro cento es convertite in cholesterol, e il es probabile que le reaction occurre principalmente durante le prime quatro horas. In casos de myxedema le production de cholesterol es reducite per un factor de quatro o cinque e a vices deveni nimis parve pro esser mesurate. Le effectos de therapia substitutive in myxedema esseva studiate, e un prompte retorno al proratas normal del synthese esseva observate. In certe patientes qui se trova sub tractamento a cortisona, le prorata del synthese de cholesterol attinge valores median de cinque vices le nivello observate in individuos normal. In certe patientes con cancere in formas avantiate un comparabile augmento del synthese de cholesterol ha essite notate.

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COMPOUND DIAPHRAGMATIC HERNIA: REPORT OF FIVE CASES *

By Charles H. Brown, M.D., F.A.C.P., Carl H. Moberg, M.D.,† and Donald B. Effler, M.D., *Cleveland, Ohio*

Considerable interest in the fields of medicine and surgery has centered around various forms of diaphragmatic hernia. This interest has been particularly stimulated by advances in the past decade that have permitted more accurate diagnosis and safer technics for surgical correction of selected cases. The typical radiographic appearance and the clinical signs and symptoms of symptomatic diaphragmatic hernias are well known to every clinician. However, in a review of the literature on the subject of diaphragmatic hernia it becomes apparent that the extent and ramifications of potential complications have not been fully appreciated. This is particularly true in a specific type of diaphragmatic hernia which we have called the "compound" hernia. This is a simple inclusive term used to describe a specific type of diaphragmatic hernia in which more than one organ has herniated through the involved foramen. This, of course, does not include the traumatic type of diaphragmatic hernia, where a rent in the diaphragm may produce herniation of a number of viscera.

Hiatus hernia is the most common hernia of the diaphragm and constitutes 70% of all diaphragmatic hernias. The incidence of hiatus hernia varies considerably with the diligence with which the investigator searches for it. Brick and Amory [1] surveyed 300 asymptomatic men more than 50 years of age and found an incidence of 1.3%. Portis and King [2] found hiatus hernias in 7.5% of 133 patients more than 60 years of age. Knothe,[3] using heavy abdominal pressure as a diagnostic technic, demonstrated an incidence of 8%; and Schatzki,[4] using colonic distention as a diagnostic technic, reported an incidence of 70% in patients more than 60 years of age. The last two diagnostic methods are too cumbersome and traumatic for general use. It is advisable, however, to obtain a roentgenogram of the stomach with the patient in the Trendelenburg position after a barium swallow; hiatus hernia is so common that any routine roentgen study of the stomach should include that view. Common etiologic factors other than those of a congenital nature include trauma to the chest or abdomen and any condition that increases intra-abdominal pressure, such as pregnancy, ascites, obesity and chronic constipation. With the aging process there

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may be a decrease in the elastic and fatty tissue at the hiatus, making the older age groups more prone to develop a hiatus hernia.

While simple hiatus hernia of the stomach is quite common, a compound hiatus hernia is extremely infrequent. This is also true of compound diaphragmatic hernias involving the foramen of Morgagni or the foramen of Bochdalek. When such a hernia does occur, however, and a large amount of viscera including stomach, portion of the large or small bowel, and a great deal of omentum are able to enter the mediastinum or a thoracic cavity, the patient eventually may suffer severe cardiorespiratory embarrassment, subsequently resulting in death. Although obstructive phenomena of the stomach or bowel have long been recognized in severe diaphragmatic hernia, we believe that the severity of the cardiorespiratory symptoms has not been appreciated, nor has the entity been recognized as a very real cause of disability and possible loss of life.

Involvement of the colon in nontraumatic diaphragmatic hernia is an uncommon occurrence. Saltzstein, Linkner and Scheinberg [5] found only 29 such cases in a review of the literature up to 1951. We wish to present five cases of diaphragmatic hernia in which the colon was involved as part of the herniated viscera; as suggested above, it is not the anatomic features of the compound hernia that are of significance, but rather it is the severity of the resultant symptoms, particularly those involving cardiopulmonary status.

Case Reports

Case 1. A 63 year old man was seen July 23, 1951, with complaints of bloating, gas and belching after meals and palpitation on exertion which had been present for 10 years. He had a dull ache across the upper abdomen associated with the bloating, and had had diarrhea with considerable mucus in the stool. He had had respiratory difficulty, with cough, dyspnea and wheezing, all his life. He also had noted paroxysmal nocturnal dyspnea for two years, orthopnea for six months, and swelling of the ankles for two weeks.

On physical examination he was cyanotic and dyspneic and had distended neck veins. Many fine râles were present in both bases, with dullness, diminished breath sounds and tactile fremitus in the left base. Expiratory wheezes were present. Blood pressure was 142/74 mm. of Hg, and pulse rate was 108. The liver was enlarged and tender three fingerbreadths below the costal margin.

An electrocardiogram showed digitalis effect and nonspecific myocardial changes. Blood urea nitrogen was 84 mg. per 100 ml. The blood count, hemoglobin, urinalysis, blood sugar, plasma carbon dioxide and serology were negative or normal.

Roentgen examination of the chest (figure 1) showed marked displacement of the cardiac shadow posteriorly and to the right. A diffuse opacity occupied the lower two thirds of the left chest. Air pockets or cystic areas with fluid levels were suggested anteriorly and superiorly in the left chest. Density in the right lower chest conformed somewhat to that of the middle lobe.

The patient was considered too ill for gastrointestinal roentgen examinations. On July 30, one week after initial examination, the diagnosis of a diaphragmatic hernia was made. Because his condition became progressively worse, surgery was performed as a last resort on August 3. At operation a diaphragmatic hernia through the foramen of Bochdalek, probably of the congenital type, was found. The

left pleural space contained all the small intestine distal to the ligament of Treitz, the right, transverse and descending colon to the sigmoid, the spleen and a large share of the omentum. The spleen and the right and transverse colon were resected and an ileocolostomy was performed. The patient died eight hours postoperatively.

On postmortem examination the following additional pathologic conditions were found: hypoplasia of the left lung, pulmonary edema and focal hemorrhage of the lung, acute congestion of liver and kidneys, porencephaly, and a small accessory ventricle of the left internal capsule area.

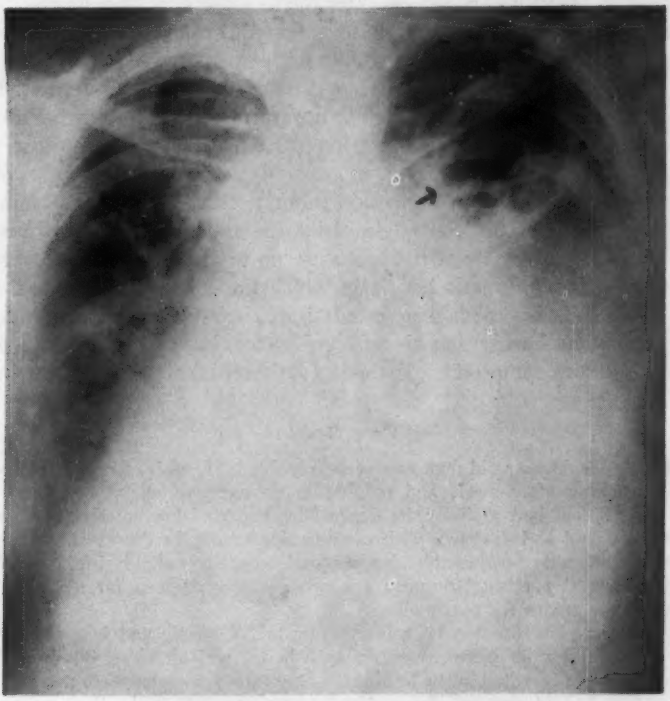


FIG. 1. *Case 1.* Roentgenogram of the chest showing marked displacement of the cardiac shadow to the right and posteriorly. A diffuse opacity occupies the lower two thirds of the left chest. Air pockets or cystic areas with fluid levels are seen. These roentgen findings were due to herniation through the foramen of Bochdalek of all the small bowel below the ligament of Treitz, the right, transverse and descending colon, spleen, and part of the omentum.

Comment: This patient undoubtedly had a congenital diaphragmatic hernia. It is difficult to understand why the condition was not discovered earlier. A physical examination or an x-ray of his chest at some time during his 63 years of life should have aroused sufficient suspicion to warrant further studies that would have disclosed his true condition. We believe that if the diagnosis had been made earlier, definitive surgery at that time would have prolonged his life for many more years.

Case 2. A 46 year old woman was seen in November, 1953, with complaints of episodes of dysphagia for six years, gas and bloating for three years, and constipation of many years' duration. For the previous six years, at intervals of every two to four weeks, bits of ingested food had lodged in the midsubsternal area; these attacks had been followed by an acute, severe pain radiating to the epigastrium and upper left quadrant. The pain lasted for from 20 minutes to four hours; as it subsided it was referred to the left infraclavicular area and down the left arm to the fingers.

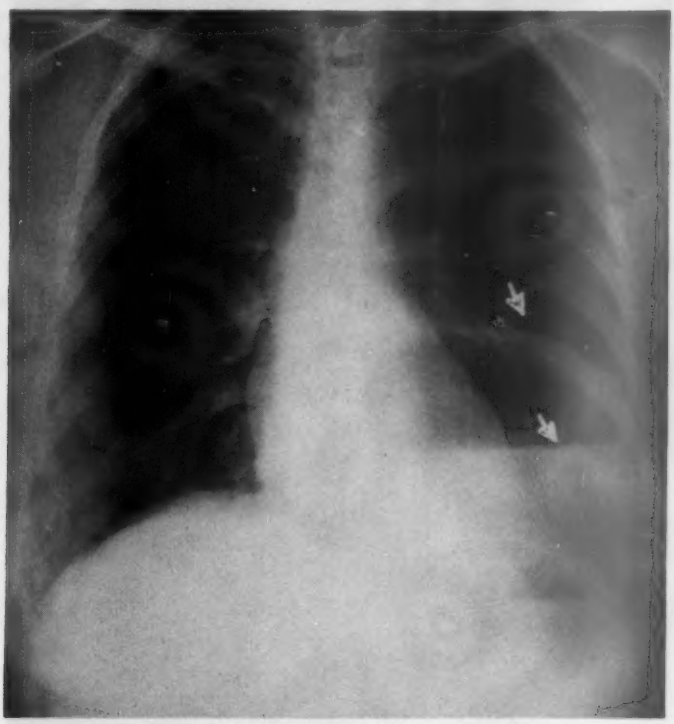


FIG. 2A. *Case 2.* Roentgenogram of the chest; the left leaf of the diaphragm is not definitely identified. Shadow of abdominal viscera is present to the level of the fourth anterior rib (upper arrow). Long fluid level is also suggestive of stomach or bowel (lower arrow).

Complete physical examination was essentially normal. Laboratory studies showed a moderate hypochromic anemia, the hemoglobin being 9.0 gm., with a cell volume of 32 c.c. Stool examination, urinalysis, blood sugar, gastric acidity and serology were negative or normal.

Roentgen examination of the chest showed the right lung field to be normal. The left leaf of the diaphragm was not definitely identified; the shadow of abdominal viscera was visible in the left lower chest to the level of the fourth anterior rib (figure 2A). The gall-bladder was normal. On barium examination a portion of the stomach was found above the diaphragm. Barium enema examination (figure

2B) showed the splenic flexure of the colon to be in the thorax, extending 10 cm. above the diaphragm, and the cecum to be inverted, with a very short ascending colon.

At operation on January 4, 1954, approximately two months after the initial examination, a large para-esophageal hiatus hernia and an esophagus of normal length were found. Almost the entire stomach and the splenic flexure of the colon were present in the thorax. The hiatus of the diaphragm admitted the surgeon's



FIG. 2B. *Case 2.* Barium enema examination; the splenic flexure of the colon is in the thoracic cavity on the left, extending 10 cm. above the usual level of the diaphragm.

fist. The stomach and colon were replaced in the abdominal cavity and the large hiatus was repaired. The patient's postoperative course was uneventful and she was discharged on January 13, 1954.

Roentgenogram of the chest postoperatively was normal. When seen six weeks after the operation, she had experienced no further discomfort.

Comment: This patient had a hypochromic anemia, as do many patients with a hiatus hernia. Some of her pain resembled angina in distribution.

She had no respiratory symptoms, but we believe that if the hernia had not been repaired respiratory symptoms would have developed.

Case 3. A 51 year old man was seen on November 15, 1952, with a complaint of "smothering" and "misery" in his right side of four years' duration. In 1948 the patient had had a minor fall which caused strangulation of a left inguinal hernia, necessitating a herniorrhaphy. Since the operation he had noted shortness of breath on exertion and orthopnea, being unable to lie flat. He had some pain along the right costal margin related to exercise and to movement of the right arm. He complained of some right abdominal pain postprandially which was associated with borborygmi and which was relieved by belching and expelling flatus or stool.

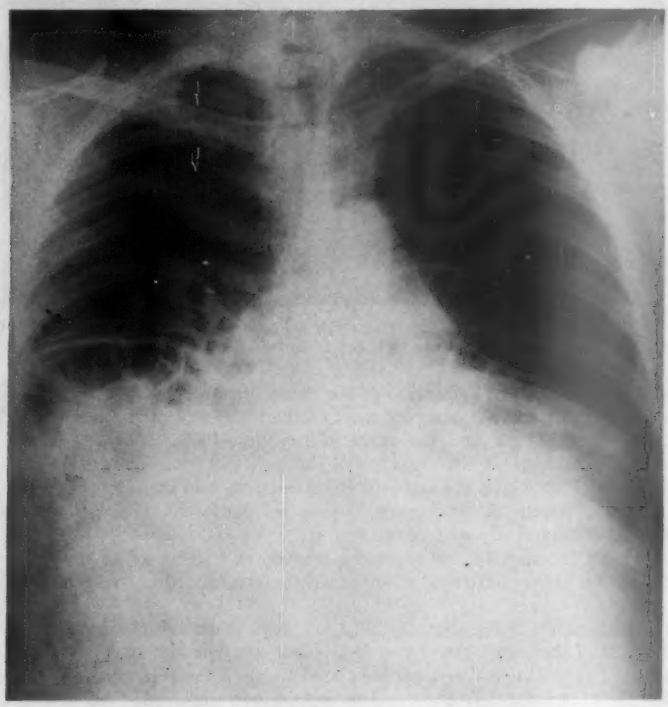


FIG. 3*A*. *Case 3.* Roentgenogram of the chest showing air-filled pockets suggestive of cysts, but which are intestinal loops of gas-filled bowel.

On physical examination there were dullness and decreased breath sounds over the right base. Bowel sounds were easily heard over the entire right chest. A recurrent left inguinal hernia and a direct right inguinal hernia were present.

Laboratory examinations showed the blood count, hemoglobin, cell volume, urinalysis, serology, blood sugar and blood urea nitrogen to be negative or normal. An electrocardiogram showed nonspecific myocardial changes.

Findings on roentgen examinations were as follows: Chest (figure 3A): Loops of gas-filled intestines were identified above the right leaf of the diaphragm and through the shadow of the heart in the midline and to the left of the midline. Barium

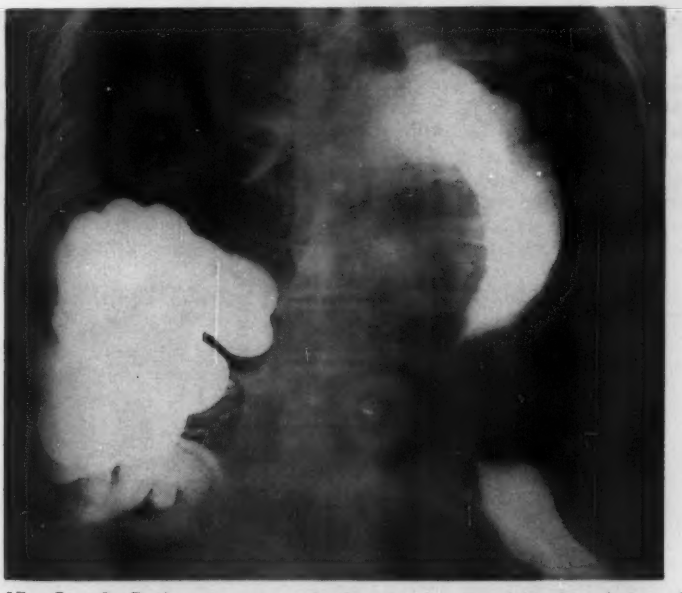


FIG. 3B. *Case 3.* Barium enema examination showing the right side of the colon herniated through the foramen of Morgagni.

swallow showed extensive herniation of the small intestine and part of the colon into the thoracic cavity, where it occupied most of the right side of the thorax. The liver was displaced downward and the right kidney anteriorly. Barium enema (figure 3B) showed herniation of the right colon through the foramen of Morgagni, a left inguinal hernia into which the sigmoid colon entered, and considerable diverticulosis of the sigmoid colon. A retrograde pyelogram disclosed marked displacement of the right kidney anteriorly and downward.

Pulmonary function studies showed a marked restriction of all segments of lung volume without hyperventilation or disproportionate reduction in breathing capacity (table 1).

At operation on November 26, 1952, 11 days after initial examination, it was found that all of the small bowel two feet below the ligament of Treitz, the ileocecal valve and the ascending colon were herniated through the foramen of Morgagni into both the right and the left chest. The hernia was repaired. An active duodenal ulcer was also found.

TABLE 1

Pulmonary Function Studies (Case 3)

Lung Volumes	Predicted	Observed
Vital capacity	3276 c.c.	1097 c.c. (51%)
Residual air (RA)	1597 c.c.	1370 c.c.
Total capacity (TC)	5323 c.c.	3277 c.c.
RA/TC × 100	30%	41%
Maximal breathing capacity (MBC), 4 min.	114.91	54.72
Resting minute vol. ventilation	6–7 L./min.	7.34 L./min.
Breathing reserve, % MBC	90%	83%
O_2 uptake, c.c./L. ventilation	40–50 c.c./L.	41.5 c.c./L.

The patient's postoperative course was uneventful and he was discharged one week after operation on ulcer management. A month later the patient was asymptomatic, had no dyspnea, was able to lie flat in bed and could eat without discomfort.

Comment: This patient's most distressing symptoms were those related to diminished pulmonary function. Before operation he had been unable to lie down and had been forced to sleep in a chair.

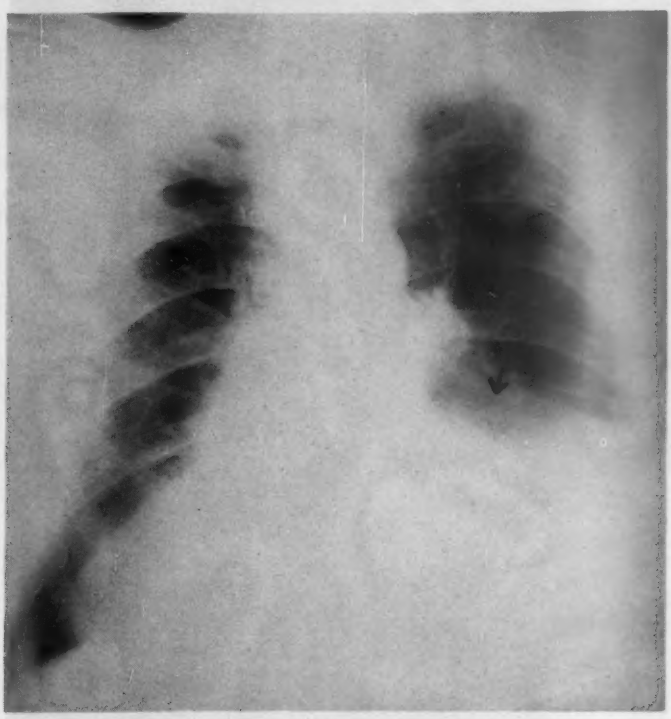


FIG. 4*A*. *Case 4.* Roentgenogram of the chest showing a bizarre picture in the lower half of the left lung field, the lower portion being homogeneous and the upper portion containing air (arrow). A rounded density is present at the right cardiophrenic angle.

Case 4. A 64 year old man was first seen on October 9, 1951, with complaints of progressive dyspnea of two years' duration, a dry cough for six months, and sharp epigastric pain immediately after eating, particularly after large meals, for two years. These symptoms had gradually increased in severity over the two year period. The abdominal distress was sometimes relieved by lying down.

On physical examination the chest was emphysematous in type, with hyperresonance except for an area of dullness and diminished breath sounds at the left base.

Laboratory studies showed a polycythemia, with a hemoglobin content of 19 gm., a red blood cell count of 6,920,000, and a cell volume of 63 c.c. The blood sugar,

liver function tests and serology were negative or normal. An electrocardiogram was normal.

Findings on roentgen examinations were as follows: Chest (figure 4A): The lower half of the left lung field was obscured by a dense shadow, the lower portion homogeneous and the upper portion containing air. A rounded density was present in the right cardiophrenic angle. A diagnosis of a large diaphragmatic hernia was made. Stomach (figure 4B): There was a large hiatus hernia into the left chest



FIG. 4*B*. *Case 4.* Roentgenogram of the stomach showing a large herniation through the esophageal hiatus with an upside-down position of the stomach.

through the normal esophageal hiatus. The stomach was in an upside-down position, with the cardiac or fundal end of the stomach in the lowest portion. On lateral films a portion of the colon was also seen above the leaf of the diaphragm. Barium enema examination (figure 4C) showed the splenic flexure and most of the transverse colon to be above the diaphragm.

Pulmonary function studies were most consistent with some degree of anatomic restriction of ventilation, in addition to some degree of lung compression or poor aeration of a small portion of the lung, which was well perfused (table 2).

At operation on November 11, 1951, approximately a month after initial examination, a herniation through the esophageal hiatus was found, the hiatus being three times normal size. The herniation included the entire stomach, most of the transverse colon, the omentum, and some of the small intestine. There was marked displacement of the heart and major vessels anteriorly. The left lower lobe of the lung was only partially expanded, due to the displacement by the herniated structures.

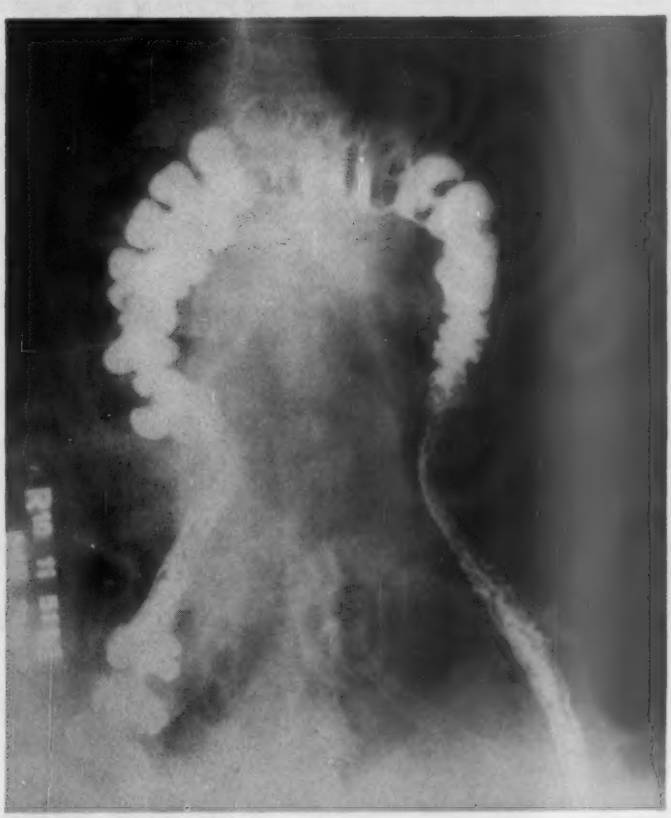


FIG. 4C. *Case 4.* Barium enema examination showing the splenic flexure and most of the transverse colon above the diaphragm.

The hernia was repaired without difficulty. The patient's postoperative course was uneventful except for a pleural reaction at the left base.

Comment: Studies showed a marked decrease in the pulmonary function in this patient that had resulted in a secondary compensating polycythemia. Any abnormality in the blood count in patients with hiatus hernia usually is a hypochromic anemia due to low-grade blood loss from conditions such as gastric erosions associated with the hernia. This patient had the unusual

TABLE 2

Pulmonary Function Studies (Case 4)

Lung Volumes	Predicted	Observed
Pulmonary Function Studies:		
Vital capacity	3.3986	2.1566
Maximal breathing capacity (MBC)	111.1 L./min.	57.6 L./min.
Resting minute vol. ventilation	7.2 L./min.	
Breathing reserve	50.4 L./min.— 87.5% MBC	
Exercise Test:		
	Rest	Post-exercise
O_2 cons.	265.55 c.c.	599.61 c.c.
Vent./min.	7.25 L.	18.17 L.
O_2 uptake	35.40 c.c./L.	33.00 c.c./L.

Arterial Blood Gases:

O_2 capacity = 21.4 vol. % = 15.7 gm. hemoglobin
O_2 content = 18.9 vol. % = 84.5% saturation
CO_2 content = 46.8 vol. %

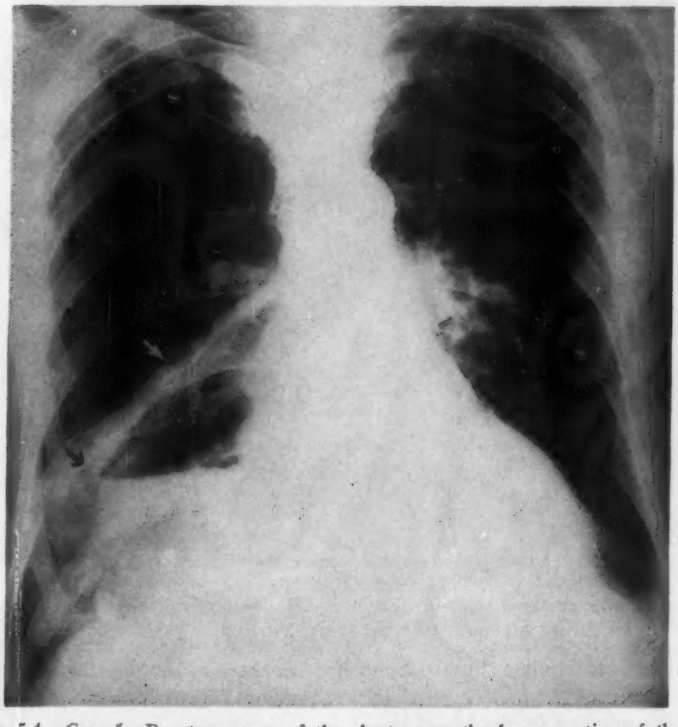


FIG. 5*A*. *Case 5.* Roentgenogram of the chest; over the lower portion of the right lung field there was considerable increased density with a fluid line (lower arrow). Below the fluid level there was a homogeneous density, while a translucent cavity appeared above it. This was due to herniation of the stomach through the esophageal hiatus.

finding of a polycythemia secondary to decreased pulmonary function and chronic lung compression.

Case 5. A 68 year old man, a physician, was seen on February 5, 1950, with a nine year history of episodes of vomiting associated with epigastric and back pain that occurred every three to six months. During the course of self-medication the patient had become addicted to narcotics and barbiturates. He had had mild bouts of cardiac decompensation, for which he took digitalis daily.



FIG. 5*B*. *Case 5.* Barium enema examination showing a large portion of the transverse colon in the thorax.

On physical examination the lungs were hyperresonant, with prolongation of the expiratory phase. Blood pressure was 180/100 mm. of Hg. Grade IV aortic and mitral systolic murmurs were present (reported to have been present since birth). There was 1 plus ankle edema. A reducible right inguinal hernia was palpated.

Laboratory Findings: The blood count, hemoglobin, blood sugar and serology were negative or normal. An electrocardiogram showed digitalis effect, with short bursts of paroxysmal auricular tachycardia.

Roentgen Examinations: Chest (figure 5A): Over the right lung field laterally there were increased density and, medially, a translucent cavity with a fluid line and some opaque shadows. This was thought to represent the cardia and fundus of the

stomach lying above the diaphragm. Stomach: The cardia of the stomach was visualized to the left of the spine and the body of the stomach to the right, both above the diaphragm. Herniation had occurred through the esophageal hiatus. Colon (figure 5B): A large portion of the transverse colon was in the thorax, and there was a marked diverticulosis of the sigmoid and descending colon.

The patient refused operation, and because of his poor condition and age it was not insisted upon.

Comment: With such a massive herniation of both the stomach and colon involved, surgery certainly would have been strongly advised had we seen the patient in 1941, when his symptoms first occurred. No medical treatment will effectively relieve such a massive hernia. This patient had recurring pain so severe that he had become a narcotic addict. If operation had been done when the massive hernia was first discovered, the patient certainly would have been much more comfortable and undoubtedly would not have become an addict.

Discussion

These five cases emphasize the varied manifestation of massive herniation of abdominal contents into the thorax and the difficulties in diagnosis (particularly well illustrated by case 1). Cardiorespiratory symptoms were severe in all cases and easily demonstrated by pulmonary function studies. In case 1 the symptoms suggested cardiac disease; in cases 3 and 4, permanent severe restriction of pulmonary function had occurred.

Roentgenograms of the chest in cases of massive diaphragmatic hernia frequently suggest the diagnosis, and in our patients they were of great value. The diagnosis can be definitely established by gastrointestinal roentgen studies, using such technics as the Trendelenburg position and the Valsalva maneuver; however, in such massive herniations as these such technics are unnecessary. No routine gastrointestinal roentgen examination should be done without search for a hiatus hernia; this can best be done by obtaining films with the patient in the Trendelenburg position. In patients in whom a hiatus hernia is suspected clinically, a Valsalva maneuver (have the patient take a deep breath, hold it and strain down) may enable the roentgenologist to demonstrate the hernia.

Hiatus hernia may cause massive hematemesis, melena or hypochromic anemia. One of our patients (case 2) had hypochromic anemia. We believe that the gastrointestinal bleeding associated with hiatus hernia is due more to gastric erosions and congestion of the venous return in the hiated portion of the stomach than to true peptic ulceration. Nonetheless, the possibility of a hiatus hernia should be thoroughly investigated in any patient with massive gastrointestinal bleeding or evidence of a chronic blood loss.

While a hypochromic anemia is common in patients with a hiatus hernia, it is unusual to find polycythemia associated with a diaphragmatic hernia. One of our patients (case 4) had a marked polycythemia that was

secondary to decreased pulmonary function. The development of the polycythemia is another indication of the great severity with which massive diaphragmatic hernias may affect pulmonary function.

In one of our patients (case 2) the distribution of pain was consistent with that seen in angina pectoris. However, as pointed out by Master, Dack, Stone and Grishman,[6] the pain was not related to exercise or to undue excitement, but rather exclusively related to meals. The duration is usually longer than that anticipated in angina pectoris and is not as a rule relieved by nitroglycerin. Differentiating the pain of hiatus hernia from that of coronary artery disease, however, may be difficult in the older patient, for Kohli and Pearson[7] have demonstrated that changes in the T-wave and RST segment can be produced by balloon distention of the esophagus. In several of their patients with significant electrocardiographic changes on exercise tolerance tests, they were able to reproduce the same changes with balloon distention of the respective hiatus hernia. Both conditions are most common in the older age group, and it is not unusual for the two conditions to be present in the same patient.

The pain with an incarcerated massive diaphragmatic hernia may be quite severe. One of our patients (case 5), a physician, became addicted to narcotics, and we have seen one other physician who also became so addicted, due to the pain associated with a hiatus hernia. Another patient (case 2) also described intense pain.

The colon symptoms due to a portion of the colon's being in the thorax may be those of irritable colon, with gas, bloating, flatulence, constipation or diarrhea. The symptoms may become more severe and be those of partial obstruction of the colon, with cramping abdominal pain, etc. We have not observed it, but these patients easily could develop complete bowel obstruction due to conditions such as torsion and edema of the herniated colon.

In contrast to the simple hiatus hernia, medical treatment has nothing to offer these patients with compound massive diaphragmatic hernias that include the colon and other organs. Any attempt at conservative management will only result in further respiratory embarrassment. We believe that these massive hernias should be corrected early surgically so that respiratory function may be restored to as nearly normal as possible; they should be corrected before respiratory function becomes so poor, as in case 1, that surgery is hazardous.

Summary

1. Five cases of compound diaphragmatic hernia have been presented in which the colon was in the thoracic cavity.

2. The diagnostic importance of pulmonary function studies has been emphasized. Serious impairment in respiratory function may result from

compound diaphragmatic hernia and may cause the patient's chief and presenting symptoms.

3. Correct diagnosis and surgical correction of the defect in such massive herniations are mandatory to reduce pulmonary disability.

SUMMARIO IN INTERLINGUA

Hernia diaphragmatic "componite" es un termino definite per nos como un typo specific de hernia diaphragmatic in que plus que un organo protrude per le foramine. Es presentate cinque casos in que le colon (in alicunes le intestino tenue) esseva in le cavitate thoracic. Como es le caso con le majoritate de hernias diaphragmatic, iste condition pote causar "inexplicate" anemia e sanguination gastrointestinal. In patientes con anemia e/o sanguination gastrointestinal le possibilitate de hernia diaphragmatic merita le plus exacte attention.

Le distribution de dolores pote parer compatibile con angina de pectore. Le dolores pote esser sever. Isto esseva le caso in duo de nostre patientes. Le un de illes deveniva narcomane. Le symptomas presentate per le colon pote esser illos de irritabilitate colonic, con gas, flatulentia, e alteration del habitudes excretori; iste symptomas pote etiam esser plus sever, i.e. illos pote simular un partial obstruction intestinal.

Serie dysfunction respiratori pote resultar de hernia diaphragmatic componite; a vices illo es le major symptoma que duce le patiente al consultation medical. Roentgenogrammas thoracic suggere frequentemente le diagnose que pote esser confirmate per le studio de roentgenogrammas gastrointestinal.

In herniationes tanto massive, le correcte diagnose del defecto e su tractamento chirurgic es imperative pro reducer le invaliditate pulmonar. Massive hernias diaphragmatic require un prompte intervention chirurgic pro restaurar in tanto que possibile un normal function respiratori ante le occurrentia de alterationes irreversibile.

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CASE REPORTS

GANGRENE OF THREE LIMBS RESULTING FROM VENOUS OCCLUSION *

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GANGRENE of the limbs resulting from venous occlusion without arterial obstruction is extremely rare. Haimovici in 1950 [1] summarized the 27 cases then reported in the literature and mentioned another. He emphasized the importance of anatomic confirmation of the patency of the arterial system in establishing the diagnosis. Gangrene was present in one limb only in 23 of the cases he reviewed, and in both lower limbs in the remaining four. Veal et al. in 1951 [2] have described 11 cases of acute massive venous occlusion, confined to one or other of the lower extremities, in which gangrene developed in two instances. These authors stress the importance of early, extreme elevation of the limb, together with rapid exercises, as a therapeutic measure.

We now report the occurrence of gangrene of both legs and one arm due to venous occlusion of uncertain origin. Patency of the arterial system was demonstrated anatomically.

CASE REPORT

A housewife, aged 42 years, was admitted to St. James's Hospital, Leeds, on December 6, 1953, in status asthmaticus of 36 hours' duration. She gave a history of recurrent attacks of bronchial asthma for 15 years. She had no other complaints, and gave no history of serious illness in the past.

Examination on admission showed a pale, slightly cyanosed, well built woman. She was breathless, wheezing and obviously distressed. The skin was moist and the temperature was 99.4° F. The pulse was regular, rate 120 per minute, and the blood pressure was 150/100 mm. of Hg. There were widespread rhonchi over both lungs and moist sounds at the lung bases. There were no other abnormal physical signs. Radiography of the chest showed some pulmonary hyperemia. The electrocardiogram was normal. The hemoglobin was 11.1 gm.%. Urine examination was negative.

Progress and Treatment: The asthma responded rapidly to treatment with intravenous aminophylline, 0.25 gm., and Neoepinine, 10 mg. orally three times a day, but fever persisted for seven days, during which time penicillin (Distaquaine), 300,000 units twice a day, was given. On December 15, nine days after admission, she complained of pain in the right calf, which was swollen and tender. Her temperature rose to 100.2° F. Thrombophlebitis was diagnosed, and treatment with an anticoagulant (Tromexan) and penicillin (Distaquaine) was started. Two days later the swelling had increased, and marked pitting edema was present up to the midthigh and down over the dorsum of the right foot. The left calf was now also tender, and edema was present below the knee. Both legs and feet were warm and no color

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changes were visible. The femoral and popliteal pulses were present and equal, but pulsation of the dorsalis pedis arteries was not detected, probably because the edema obscured it. The fever continued, and on December 19 Aureomycin, 250 mg. every six hours, was substituted for the penicillin and continued for 10 days. The end of the bed was raised and leg exercises were begun. On December 29 considerable improvement had resulted: the pain had disappeared, the temperature was normal and the edema was much less. Anticoagulant therapy was stopped two days later, the prothrombin index during treatment having varied considerably from day to day, the lowest reading having been 47%.

Physiotherapy was continued, and satisfactory progress occurred during the following 10 days. The patient had indeed reached the stage where she was fit for discharge from hospital when, on January 11, 1954, relapse occurred. The temperature rose to 101.2° F. and the pain and edema recurred, appearing first in the left calf and the following day in the right calf. The edema rapidly increased, involving the whole of the right lower limb and extending to the midthigh on the left side. Edema also appeared over the lower abdominal wall and sacrum, and a few distended veins were seen over the lower abdomen. The end of the bed was elevated and physiotherapy continued. Heparin and, later, Tromexan were given, with satisfactory effects on blood coagulation. Penicillin and, later, Aureomycin were also prescribed, but with little effect on the pyrexia.

On January 21 the patient developed an acute attack of pain over the right lower chest and a slight hemoptysis occurred. The temperature was 102° F., and a pleural rub was audible at the right lung base. Pulmonary infarction was diagnosed. The edema of the lower limbs persisted, and both feet were now observed (January 21) to be intensely cyanotic. The feet were still warm and the popliteal pulse was present in the left side, but other pulses were not palpable in the lower limbs because of the massive edema. The discoloration rapidly spread up the limbs and lines of demarcation became apparent—on the right side at the midcalf region, and on the left side at the junction of the middle and lower thirds of the thigh. Investigations carried out at this time gave the following results: Radiography of the chest showed no abnormal features. Prothrombin time, 51 secs. (prothrombin index, 29%). Sedimentation rate (Westergren), 19 mm. in the first hour; hemoglobin, 11.0 gm.%; red cells, 4,310,000 per cubic millimeter; white cells, 24,000 per cubic millimeter; differential white cell count: neutrophils, 74%; eosinophils, 12%; lymphocytes, 12%; monocytes, 2%. The blood film showed evidence of mild hypochromic microcytic anemia, neutrophil leukocytosis and eosinophilia. The blood urea nitrogen was 14 mg.%. Blood culture was negative after seven days' incubation. A catheter specimen of urine showed no abnormality. Pelvic examination was negative.

Morphine was needed to assuage the severe pain in the legs. On January 23, two days after the color changes in the lower limbs were noted, the right forearm and hand became edematous and blue. A sharp line of demarcation appeared 3 inches below the right elbow joint.

Anticoagulants and antibiotics were continued, and the affected limbs were raised continuously at an angle of approximately 30 degrees to the horizontal. However, the edema persisted, the temperature remained elevated, severe pain continued and large bullae appeared over the affected parts. The discoloration of the affected limbs remained unchanged, and the feet and right hand became cold and gangrenous. Hematuria and hemoptysis of mild degree, with a progressive anemia, were observed terminally, and the patient died on February 5, 1954. Further investigations carried out within the two weeks prior to death were as follows: Urine urobilinogen, 0.38 mg.%. No excess of porphyrins was detected. Hemoglobin, 4.7 gm.%; reticulocytes, 6%; white cells, 26,000 per cubic millimeter. Differential: white cell count:

myelocytes, 1%; metamyelocytes, 2%; neutrophils, 85%; eosinophils, 1%; lymphocytes, 8%; monocytes, 3%. Platelets, 210,000 per cubic millimeter.

Post Mortem: The body was that of a well nourished, middle aged woman. There was extensive gangrene of the left foot extending up to just above the knee, of the right foot extending to the midcalf, and of the right hand extending to just above the wrist (figure 1). Shallow sacral bedsores were also present. The right breast contained a small nodule, about 1.5 cm. in diameter, and also evidence of cystic hyperplasia.

Pleural cavities and peritoneum: Normal. *Trachea and bronchi* contained some rather viscid mucus. *Lungs:* The right lower lobe was covered with fibrinous exudate, part of which showed hemorrhage. Branches of the right pulmonary artery in the lung contained small white thrombi. The lung substance was congested and somewhat collapsed. The left lung showed small areas of early bronchopneumonia. *Pericardium:* Normal.

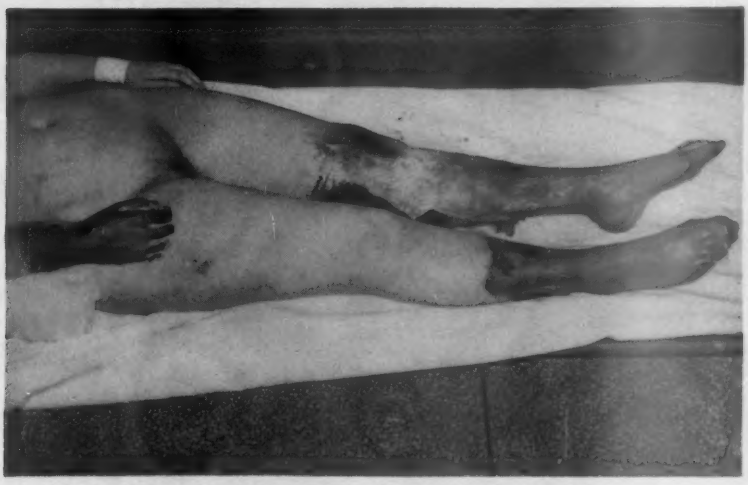


FIG. 1. Postmortem photograph showing the distribution of the gangrene.

Heart: The heart weighed 200 gm. The myocardium was extremely soft and pale. The valves were normal; the tricuspid was a little dilated. *Coronary arteries* were slightly atheromatous but patent. *Aorta* was moderately atheromatous.

Esophagus, stomach and intestines appeared normal. There was a small calcified lymph node in the mesentery. The *spleen* weighed 200 gm. and was congested. *Thyroid* was hyperplastic. *Bladder* showed a moderate degree of cystitis. *Uterus* was normal. *Cervix* showed a large erosion. The uterus was adherent to the pelvic colon, and a mass of old adhesions surrounded both ovaries and tubes.

The liver, gall-bladder, adrenals, pituitary, pancreas, kidneys, ureters and brain were normal in appearance.

Both femoral and iliac veins were thrombosed up to the junction of the common iliac veins. The inferior vena cava and portal veins were free of thrombus. Small veins around the pelvic organs were thrombosed, and some of the pelvic muscles appeared soft and partly necrotic. Numerous small veins in the lower limbs were examined and found to be thrombosed. The femoral arteries were followed throughout their course, and neither they nor the tibial arteries showed evidence of thrombus



FIG. 2. Tissue from floor of pelvis, showing widespread venous thrombosis and patency of the arterial system. × 50.

formation. The right radial and ulnar arteries were examined at the wrist and found to be free of thrombus. The brachial vein and the proximal ends of the ulnar and radial veins did not show any thrombosis, although examination of the veins in the forearm was rendered difficult by considerable adipose tissue, edema and gangrene.

Microscopic examination revealed hypertrophy of the bronchial muscle and emphysema. Thrombi of varying ages were seen in the branches of the pulmonary artery, some recent and others organized. Congestion and edema of the lungs were widespread, and part of the right lung was infarcted.

Pelvic veins were found to contain recent and organized thrombi, but arteries and arterioles were patent (figure 2). A few lymphocytes were seen scattered in the vessel walls, but no real evidence of inflammation was to be seen. A few fibers of pelvic muscle were pale staining and probably in an early stage of necrosis. A specimen of the left femoral vein showed the lumen to be filled by thrombus, the outer part of which was organized and partly recanalized. Some groups of lymphocytes were seen in the organized thrombus, but there was no evidence of inflammation.

The thyroid showed changes of colloid goiter with a small hyperplastic nodule, the pancreas was slightly fibrosed, and the breast nodule was seen to be a simple intracanalicular fibroadenoma. There were no other abnormal findings on histologic examination.

Discussion

The diagnosis of gangrene of venous origin must rest on the demonstration of venous occlusion without any evidence of arterial obstruction. This may be achieved by arteriography or by postmortem examination. In the patient reported here, naked-eye examination of the arteries of both legs and the right arm at autopsy showed no abnormality. Histologic evidence of patency of the arterial system was obtained from examination of sections of necrosing tissue taken from the floor of the pelvis (figure 2). There was extensive phlebothrombosis of the veins of the legs and pelvis, but thrombosis of the arm veins was not demonstrated, probably for technical reasons.

The clinical course of the illness was similar to the description given by Haimovici. An initial phase of "white" phlebothrombosis was followed by prolonged "blue" phlebothrombosis. This phase was characterized by edema, purple cyanosis and extreme pain. The temperature of the cyanotic extremities remained normal until the terminal stages. In the upper limbs there was no phase of painless white edema; painful cyanotic edema developed overnight. There was a clear-cut demarcation line between the areas of intense cyanosis and normal skin in each limb.

It seems likely that the thrombosis in this patient resulted from a combination of factors, the two most apparent being venous stasis from bed-rest and low grade pelvic infections from a cervical erosion. The autopsy findings support the contention of Fontaine and Pereira [3] that this form of gangrene follows rapidly upon venous stagnation when the return of the circulation is completely blocked. Haimovici states that in eight of the 27 cases he analyzed, concomitant simple uncomplicated venous thrombosis affecting other extremities was also noted. The widespread gangrene in the present instance reflects the distribution and severity of the thrombosis, and it is of interest that such extensive thrombosis of the arm veins should occur while the patient was well under the influence of an anticoagulant drug (Tromexan). Physiotherapy and elevation of the bed had no effect on the widespread circulatory disturbances in this par-

ticular patient, but the more vigorous exercises together with extreme elevation of the limbs suggested by Veal et al.[2] might possibly be more effective.

Summary

1. A patient with gangrene of both legs and the right arm resulting from venous occlusion is described.
2. The clinical diagnosis of gangrene resulting from venous occlusion was confirmed by the postmortem demonstration of a patent arterial system.
3. The mechanism and treatment of the condition are discussed.

Summario in Interlingua

Un patiente feminin de 42 annos de etate disveloppava thrombophlebitis del sura dextere durante que illa esseva sub tractamento pro stato asthmatic. Le attacco initial del thrombophlebitis se resolveva intra 14 dies, sed 10 dies plus tarde il habeva un recurrentia que afficeva ambe gambas e se diffundeva rapidemente. Edema massive se extendeva usque al abdomine inferior. Ancora 10 dies plus tarde ambe pedes deveniva intensemente cyanotic e multo dolorose. In le curso del sequente dies gangrena appareva. In le gamba sinistre le gangrena se extendeva usque al medietate del femore; in le gamba dextere, usque al medietate del sura. Duo dies plus tarde le bracio inferior e le mano al latere dextere deveniva subitemente edematose e gangrenose. Tractamento con anticoagulantes e antibioticos remaneva inefficace. Il habeva repetite infarcimentos pulmonar, e le patiente moriva.

Le examine post morte monstrava gangrena extense in ambe pedes e in le mano dextere. Le venas iliac e femoral esseva thrombotisate, sed le systema arterial esseva patente. Nos discute le mechanismo de gangrena a origine venose.

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SPLENIC INFARCTION ASSOCIATED WITH HIGH ALTITUDE FLYING AND SICKLE CELL TRAIT *

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Recent articles have emphasized a clinical syndrome of splenic infarction associated with high altitude flying and sicklemia.[1, 2, 3] These articles have recorded several Negro patients suffering from a syndrome previously thought to be rare. The military and economic implications of Negroes flying at high

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altitudes in unpressurized cabins have been discussed elsewhere. The question of splenectomy as the treatment of choice remains unanswered.

It is the purpose of this paper to report one additional patient with sickle cell trait and a small splenic infarct in which conservative therapy was successful.

Case Report

A 22 year old Negro male corporal was admitted to the U. S. Army Hospital, Fort Carson, Colorado, on October 28, 1954. His chief complaint was pain in the left upper quadrant of approximately 72 hours' duration. The patient had returned via boat from Korea on October 25 and stated that he had been in good health. At 10 p.m. on October 25 he boarded a commercial DC-3 airplane in Seattle, Washington, for Colorado Springs. A check with the commercial airline revealed that this airplane was not pressurized. The flight was over the Rocky Mountains. The patient had been in the air approximately four to five hours when he noted abdominal distention and increased flatus. This was followed by chilly sensations, a stiff neck, and a dull pain in his left upper quadrant. He became nauseated and tried unsuccessfully to vomit. The pain in the left upper quadrant increased in severity and was described as a dull, aching sensation, which was not pleuritic or colicky. The pain seemed to increase in severity throughout the flight.

Past History: The patient denied any symptoms or familial history compatible with sickle cell anemia. He had never been in an airplane before.

Physical Examination: The temperature was 99.4° F.; pulse, 86 per minute; blood pressure, 142/96 mm. of Hg. The patient appeared somewhat toxic. The conjunctivae and nail beds were normal. The abdomen was moderately distended, with decreased bowel sounds. The patient was extremely tender in the left upper quadrant, with mild rebound and rigidity in that area. Percussion revealed dullness in the left upper quadrant, but no definite mass could be palpated. There was no evidence of scarring in the pretibial areas, and the remainder of the physical examination was normal.

Laboratory Studies: X-ray of the chest was normal. Flat plate of the abdomen and upright film for free air revealed scattered, distended loops of small bowel. The admission white blood count on October 28 was 11,600, with a slight left shift. Hemoglobin was 14.2 gm. The sedimentation rate was moderately elevated. A malaria smear failed to reveal evidence of parasites. The serologic test for syphilis was normal. The admission urinalysis was normal. Subsequent urines for bile and urobilinogen were negative. The white blood count on October 30 was 24,200 with 83% neutrophils, 14% lymphocytes, 3% monocytes and 15.1 gm. of hemoglobin. The reticulocyte count on that date was 5.8%, and hematocrit was 44. On November 1 the total bilirubin was 0.88 mg.%, with a 1 minute direct of 0.20 mg.% and a 15 minute total direct of 0.22 mg.%, and an indirect of 0.66 mg.%. Sickle cell preparation revealed 90% of the red blood cells sickling after 24 hours. Sodium, potassium, chloride and CO_2 were within normal limits. On November 1 the white blood count was 16,350, with 71% neutrophils, 20% lymphocytes, 2% monocytes, 2% eosinophils and 5% bands. The patient had 13.8 gm. of hemoglobin. Culture of puncture aspirations of the peritoneum failed to reveal evidence of growth. A smear of peritoneal fluid, removed by paracentesis, revealed 80% polymorphonuclear leukocytes, the other cells being monocytes, mesothelial cells and lymphocytes. These findings were believed consistent with acute peritonitis. Studies of red blood cell osmotic fragility were normal. There was no evidence of spherocytosis.

Electrophoretic hemoglobin studies revealed a pattern characteristic of sickling trait. S-type hemoglobin was predominant. The fetal hemoglobin was within normal limits.

Hospital Course: Wangensteen suction was instituted and the patient was started on penicillin and streptomycin. On October 29 the patient was afebrile and stated he felt much improved. The rigidity and tenderness and the questionable mass in the left upper quadrant persisted. On the afternoon of October 29 the patient was subjected to an exploratory laparotomy. The peritoneum and bowel were entirely within normal limits. The spleen appeared two and one-half to three times its normal size and was a deep purple color. On the inferior border of the spleen was a raised firm area approximately 6 by 4 cm. This appeared to extend into the depths of the spleen. There was no evidence of peritonitis, and the spleen was not removed. Postoperatively the patient's course was uneventful, and he left the hospital on November 16 to return to civil life.

Conclusions

An additional case is presented of splenic infarction in a Negro with sickle cell trait, precipitated by high altitude flying in an unpressurized cabin. The sickle cell trait was definitely established by hemoglobin electrophoretic patterns. The patient was treated without splenectomy, even though abdominal exploration was performed. With increasing awareness of this syndrome, particularly with the demonstration of sickling, conservative therapy is feasible and successful. This patient confirms the recent suggestion of Motulsky [2] that sickle cell trait can be affected by anoxemia producing hemolysis and splenic infarction.

Acknowledgment

Dr. Arno G. Motulsky of the University of Washington, Seattle, Washington, was responsible for the electrophoretic hemoglobin determination mentioned in this report.

Summario in Interlingua

Un negro mascule de 22 annos de etate se presentava al consulta con sever dolores in le quadrante abdominal sinistro-superior. Le patiente habeva essite sin symptomas ante un volo a grande altitude in un aeroplano non-pressurisate. Al tempore de su admission al hospital ille habeva febre, leucocytosis, e un massa in le quadrante sinistro-superior. Roentgenogrammas abdominal a platta plan revelava le presentia sporadic de distendite ansas in le intestino tenue. Preparatos drepanocytic monstrava drepanisation de 90 pro cento del erythrocytos post 24 horas. Laparotomia exploratori indicava le presentia de splenomegalia e de un infarcimento splenic de circa 6 per 4 cm. Splenectomia non esseva executate, e le patiente recuperava sin incidente. Studios electrophoretic del hemoglobina revelava un configuration typic pro le character drepanocytic.

Iste caso confirma le conception que le character drepanocytic pote esser afficite per anoxemia, con le resultato de hemolyse e infarcimento splenic. Quando iste syndrome es recognoscite, specialmente per demonstrar drepanisation, therapias conservative es applicabile e splenectomia pote esser evitate.

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TREATMENT OF TOXOPLASMOSIS WITH PYRIMETHAMINE (DARAPRIM) AND TRIPLE SULFONAMIDE *

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IN the short space of 16 years since toxoplasmosis was first recognized as a disease in human beings, great strides have been made in delineating the various clinical syndromes, pathology and diagnosis of the disease. A dynamic interest in all the clinical and investigative aspects of this disease continues to reduce the gaps in our knowledge. Of the unsolved clinical problems in toxoplasmosis, the need for effective therapy is one of the greatest. While extensive laboratory investigation has disclosed agents of modest efficacy, the paucity of cases, especially those recognized sufficiently early, has made clinical corroboration difficult.

We recently observed a laboratory technician who contracted toxoplasmosis while working with virulent *Toxoplasma gondii* in the performance of the Sabin-Feldman "dye-test" and other procedures at the Laboratory of Tropical Diseases, U. S. Public Health Service, Memphis, Tennessee. As a result of this circumstance it was possible to establish the diagnosis early and institute therapy. It is the purpose of this paper to present this case in detail and to review briefly the experimental and clinical experience in the therapy of toxoplasmosis. Since excellent reviews of the entire subject of toxoplasmosis have been published in the literature, no attempt will be made to duplicate these.

CASE REPORT

This 42 year old white female laboratory technician was acutely ill upon admission to the hospital on February 8, 1954. For the preceding year the patient had been working on an experimental toxoplasmosis project at the Laboratory of Tropical Diseases, Public Health Service, Memphis, Tennessee, which involved the direct handling of contaminated materials in the performance of the "dye-test" of Sabin and Feldman, and the inoculation of animals.

The patient had been well until early January, 1954 when she noted weakness and fatigability of her arms and shoulders. About a week later muscle cramps and fasciculations involving her arms and legs appeared. She was extremely tired when first arising in the morning but would improve after some activity. Starting on January 14, the patient began to feel feverish and her temperature was elevated to 100° F. in the afternoon. At this time she began to experience drowsiness, and when not occupied she would fall asleep. A thorough examination on January 27 revealed no abnormality except low grade fever. The following day the patient first noted a painful and tender mass in the right groin, and on February 4 a painful and tender nodule in the right side of the neck appeared. By this time all of the patient's symptoms had become more severe and fever was continuously present. Following a shaking chill on February 7 her temperature rose to 104° F. During the latter part of her illness her usual dry cough became more severe and slightly productive. Anorexia had been present for three weeks prior to admission and she had lost 10

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pounds in weight. On the day of admission a severe frontal headache was present. A small red skin nodule had appeared on the thigh on January 23.

This patient had a long history of sinusitis for which sinus irrigations had been performed on two occasions in December, 1953. Complete evaluation had failed to demonstrate the cause of an episode of rectal bleeding in January, 1953.

At the time of admission to the hospital the patient was alert and coöperative. She coughed frequently. Temperature was 101.8° F.; pulse, 110; blood pressure, 110/70 mm. of Hg. There was a chain of firm, tender, freely movable nodes, 0.5 to 2.0 cm. in diameter, in the right posterior cervical region extending into the supraclavicular area. There was a similar node, 2.0 cm. in diameter, in the right inguinal area, and a few slightly enlarged nodes in the left posterior cervical chain. There was slight spasm of the right posterior cervical muscles. There was a mod-

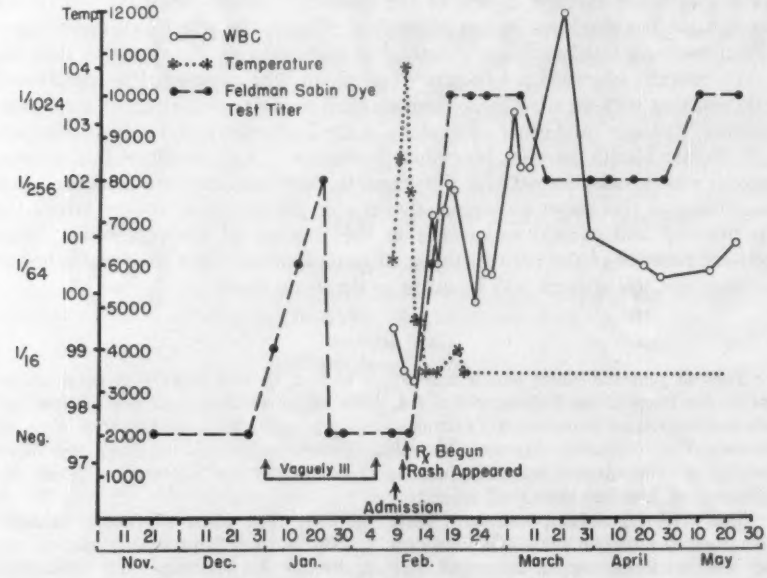


FIG. 1. Clinical course of patient.

erate amount of postnasal drip. The lungs were clear to percussion and auscultation. The heart was not enlarged and the sounds were of good quality. The liver, spleen and kidneys were not felt. No rash was present. There was a 1.0 cm. red cutaneous nodule on the right thigh. Neurologic examination was completely within normal limits. There were no other significant physical findings.

On February 8 the white blood count was 4,500; 70% polymorphonuclears; 28% lymphocytes, 2% monocytes; red blood cells, 3.7 million; hemoglobin, 11 gm.; hematocrit, 26%; sedimentation rate, 46 mm. Repeat white blood counts showed a leukopenia as low as 3,200, with an essentially normal differential until the period from February 15 to March 5, when the total leukocyte count was normal but there was a lymphocytosis ranging from 50 to 62%. Subsequent total leukocyte counts were normal except for one elevation to 12,350, and the differentials were normal (figure 1). The red blood cells rose to 4.8 million on May 24, and the hematocrit on the same date was 44%. The sedimentation rate (Wintrobe) rose as high as 49 mm., fell to

20 mm. on March 3, and then gradually rose to 40 mm. on March 16 and fell to 32 mm. by the end of the follow-up period. Spinal fluid on February 9 was negative. Liver function tests were within normal limits except for a slight elevation of the thymol turbidity to 8 units on March 1; on April 9 it was 5.1 units. The total serum protein on February 9 was 4.4; albumin, 2.9; globulin, 1.5. On March 1 the total serum protein was 5.6; albumin, 2.4; globulin, 3.2; and on subsequent occasions normal. Blood sulfonamide level on February 18 was 19 mg.%. Urinalyses and the blood serologic test for syphilis were negative. Blood cultures, serum electrolytes, nonprotein nitrogen and fasting glucose were normal. Agglutinations for typhoid, brucellosis, rickettsial diseases and infectious mononucleosis were within normal limits.

Serial electrocardiograms throughout the course of the illness and convalescence were normal. An x-ray bone survey was negative. Sinus x-rays revealed clouding of both maxillary sinuses. Serial chest x-rays revealed no abnormality. An electroencephalogram on March 19 and again on May 19 was within normal limits.

Because of the nature of the patient's work, the Sabin-Feldman dye-test for toxoplasmosis had been performed at approximately monthly intervals on her serum, starting from April, 1951. The test results had usually been an undiluted positive, with occasional tests reading negative or positive at a 1:4 dilution through November 23, 1953. The titer rose to 1:16 on January 4, 1954, and on January 22 the test was clearly positive in a dilution of 1:256 (figure 1). The titer fell to an undiluted positive reaction on January 25 and January 29, which tests were independently checked by two laboratories. The titer rose again to 1:64 on February 15 and to 1:1024 from February 18 through March 5. From March 15 through April 27 the titer was recorded as positive in a dilution of 1:256. The two tests since that time, the last on May 24, were positive in a dilution of 1:1024. Complement fixation tests on the patient's serum were performed by the Immunology Section, Laboratory of Tropical Diseases, National Microbiological Institute, Public Health Service. Nine tests from February 11 to April 26 were all negative; specimens for May 10 and May 24 were positive 2 plus, and the specimen of June 1 was positive 1 plus.

The day following admission the enlarged tender right inguinal lymph node was excised. Part of the specimen was retained for histologic examination and part was ground in saline and injected intraperitoneally into three mice. Autopsy of these mice following their deaths on February 15 and February 16 revealed numerous *Toxoplasma gondii* in the tissues. Mice injected intraperitoneally on January 25 with the patient's blood did not die and, when sacrificed, were negative for *toxoplasma*. Two of three mice injected with the patient's blood on February 10 died on February 19 and February 20, and *Toxoplasma gondii* were present. None of the mice injected with the patient's spinal fluid on the same date showed evidence of toxoplasmosis. Sections of the excised gland revealed reticuloendothelial hyperplasia, distention of sinusoids and focal necrosis; there was no evidence of parasites.

Following admission to the hospital the patient continued to be acutely ill and febrile. On February 10 the temperature rose to 104° F., and a rash appeared consisting of maculopapular discrete red lesions scattered on the lateral walls of the thorax, abdomen, thighs, shoulders and upper arms. At this point it was felt that toxoplasmosis was extremely likely and treatment was started. Triple sulfonamides,* 3 gm. initially and 1 gm. every four hours, were administered. Pyrimethamine (trade name, Daraprim), 50 mg. initially, 25 mg. in six hours, and then 25 mg. daily, was also given. Therapy was continued for 14 days.

The day following onset of treatment the patient was definitely less ill. The fever was lower, the nodes were less tender, her cough had subsided, and the rash had begun to fade. Rapid general improvement continued. Her temperature on

* Consisted of equal parts of sulfadiazine, sulfamerazine and sulfamethazine.

February 12 was 99° F. and thereafter was normal. By February 16 only a few scattered fading skin lesions remained, which cleared completely by February 20. At this time the cervical nodes were still definitely abnormal, but by February 28 only a 0.5 cm. node in each posterior cervical chain could be considered abnormal. These nodes regressed only slightly during the remainder of the period of observation. Ambulation was started on March 3 but progressed slowly because of weakness and pain in the legs which had definite hysterical features. Following discharge from the hospital on March 23 the patient continued to complain of weakness and muscular aching, particularly in her legs. She reported a low grade fever on three occasions within three weeks following discharge which was not confirmed upon follow-up examination. It was felt that many of the patient's complaints were functional in nature. After return to work on April 28 she was greatly improved, asymptomatic, and weighed 110½ pounds. Careful ophthalmologic follow-up during the period of convalescence revealed no abnormality.

Discussion

A high index of suspicion prompted by the patient's occupation, combined with the availability of personnel familiar with the disease, and the availability of laboratory technics for confirming the diagnosis, made possible the early diagnosis in this patient. Upon the appearance of the rash the clinical picture was felt to be typical enough to warrant the institution of therapy in the acutely ill patient before the diagnosis was positively established. The diagnosis was subsequently proved by the death of mice injected with the patient's blood and lymph node, and the identification of toxoplasma in their tissues. This was confirmed by the marked elevation in the titer of the dye-test.

This patient's duties involved the handling of virulent organisms under protective technics similar to those used in virus investigations. Following a fatal laboratory infection in 1951, maximal precautions had been instituted and critically evaluated at intervals. No history could be obtained from the patient of a break in technic or accidental contamination. In the known laboratory infections the mode of transmission has been obscure, except in one case reported by Strom,[1] in which infection followed pricking by a contaminated needle. Toxoplasma could not be recovered from laboratory animal ectoparasites collected from the laboratory following this infection. While there is little evidence to support oral inoculation of toxoplasma as the usual means of human transmission of the disease, it would appear as the most feasible mode in this case.

The patient's job permitted the unusual opportunity of following her dye-test titer from April, 1951. The titer showed a significant rise early in the illness, followed by a diversion to the pre-illness level during the period from January 25 until February 15, 1954. The test has remained strongly positive since that time. No satisfactory hypothesis has yet been formulated to account for the fugitive positive serologic findings early in the illness. The delay in the development of a complement fixation titer was more marked than in most reported cases.

Although the dye-test may be an important aid in establishing a diagnosis of toxoplasmosis, it would seem that in this case, as in some others previously reported, the dye-test titer does not become permanently elevated until fairly late in the course of the disease. Animal inoculation studies must also necessarily take considerable time, so it is clear that the diagnosis must be made upon clinical grounds if treatment is to be instituted early.

The rapid symptomatic improvement and lysis of fever following treatment with pyrimethamine and triple sulfonamide would suggest a therapeutic response. A spontaneous remission, however, cannot be excluded. In our opinion the response in this case to treatment would appear to confirm the response of experimental animal toxoplasmosis to pyrimethamine and sulfonamides. The slow resolution of lymph nodes, the history of fever after discharge from the hospital, and the incomplete symptomatic recovery leave room for speculation as to the persistence of a chronic infection for some weeks or months after the apparent therapeutic response.

Review of Therapy

The therapeutic challenge of toxoplasmosis has resulted in extensive animal experimentation to obtain effective agents. The agents found to be of sufficient efficacy to consider of potential usefulness in human beings are the sulfonamides, the sulfones, possibly chlortetracycline (Aureomycin) and, more recently, pyrimethamine.

As early as 1941 Sabin and Warren [2] demonstrated the activity of the sulfonamides against toxoplasmosis in mice. Many other investigators have repeated this work; while the results have varied from merely delaying death in animals to a substantial percentage of cures, the effectiveness of the sulfonamides has been confirmed with the exception that Cross [3] found sulfadiazine inactive. The divergence in results of the various investigators can best be attributed to such differences in technic as size of inoculation, mode and time of inoculation, and mode of drug administration, as well as variation in virulence of different strains of toxoplasma.[4] Of the sulfonamides tested, Eyles and Coleman [5] found sulfadiazine, sulfamerazine and sulfamethazine the most efficient antitoxoplasmic agents tested and effective in mice at blood levels attainable in man. Further experimentation with mixtures of sulfonamides is needed to amplify the preliminary favorable results of Knapp.[6] The work of Eichenwald,[7] indicating that hyperimmune serum combined with sulfadiazine resulted in considerably greater mouse survival than with either agent alone, is worthy of further study.

An advance of possible significance was made when the 2:4-diamino-pyrimidines were found to be effective against animal toxoplasmosis.[8, 9] Pyrimethamine (2:4-diamino-6-(p-chlorophenyl)-5-ethyl pyrimidine), the most active compound, was found to be at least as effective as sulfadiazine, if not more so. Since the maximal tolerated dose was close to the effective dose, the therapeutic efficiency of the compound was low. The possible value of pyrimethamine as an effective agent was greatly enhanced by the demonstration of synergism between it and sulfadiazine.[10] The combined therapy produced proportions of mice cured far greater than with any other drugs tried in animal experiments.

There is ample evidence to confirm the antitoxoplasmic effect of the sulfones,[11, 12] the only other group of chemotherapeutic agents of any significance. Although confirming this activity, one of us (D.E.E.) has demonstrated a far more favorable action in experimental animals for sulfadiazine as compared with the sulfones. Biocca and Nobrega [13] have made the undocumented claim of having successfully treated a case of human toxoplasmosis with a sulfone drug. The evidence to date warrants further study of the sulfones, particularly in combination with other agents.

The antibiotics have been extensively studied. Penicillin [14] and streptomycin [15] have been found by a number of investigators to be totally without effect in experimental toxoplasmosis. Although oxytetracycline, chloramphenicol, tetracycline and fumagillin did prolong the survival of laboratory animals slightly, only chlortetracycline has shown sufficient activity to make it of more than passing interest.[16, 17] The results of various investigators with chlortetracycline have varied widely. It appears that the dosages necessary for effect in animals would not be feasible in human therapy. More recently, puromycin [18] and erythromycin [19] have been shown to have limited effect in experimental toxoplasmosis but are of dubious practical value.

The therapy of human toxoplasmosis presents several inherent problems. The acute cases available for study have been few, and the diagnosis has often been made too late to institute controlled therapy. The natural wide variation in the severity of the disease and the outcome further complicates evaluation. In the congenital form of the disease the usual extensive organic damage severely limits what effective therapy might accomplish, and also makes evaluation of results difficult.

The majority of the acute cases of toxoplasmosis have received sulfonamides at some time in their course, but only a few have had what could be considered adequate therapy. The six year old boy with toxoplasmic encephalitis reported by Sabin [20] was treated with sulfanilamide for eight days without effect. The patient treated by Kass [21] did not respond to sulfadiazine in a dosage of 6 gm. daily for two weeks. Brennan's[22] unusual case, the diagnosis of which may be subject to doubt, improved during the period that sulfadiazine was given. The most favorable response is that of the case reported by Robinson,[23] in which the diagnosis was based on identification of the organism in the spinal fluid, which appeared to respond to treatment with sulfathiazole and emetine initially and following a relapse. The results of treatment of congenital toxoplasmosis are extremely difficult to interpret because of preëxisting organic damage.

There is ample clinical evidence that penicillin and streptomycin are without effect in toxoplasmosis.[21, 23, 24, 25, 26] In the few cases that have received chlortetracycline there was no favorable effect. Sexton's [27] patient was desperately ill at the time chlortetracycline was started, four days before death. Kass [21] treated his patient with chlortetracycline, 2 gm. daily for nine days, without evidence of effect. Further experience with this drug is necessary before a definite opinion can be given. A serologically diagnosed case,[28] mistaken for typhoid fever and as a result treated with chloramphenicol in a dose of 2.5 gm. daily for 20 days, showed what appeared to be a prompt response to therapy, evidenced by a remission of symptoms and defervescence on the third day of treatment. It is not possible to distinguish between a therapeutic response and a spontaneous remission in this case.

On a basis of clinical trial the only effective agents are the sulfonamides with emetine, as demonstrated by Robinson's report, and chloramphenicol, as described by Meira.[28] The value of these reports would be greatly enhanced if the diagnosis could have been proved by animal inoculation. The efficacy of combined pyrimethamine and sulfonamide therapy, as demonstrated in animal toxoplasmosis and confirmed by the favorable response of our patient, indicates this to be the current treatment of choice for toxoplasmosis. This conclusion is

supported by the recent report of Ryan et al.[29] of favorable response of ocular toxoplasmosis to these agents.

Summary

A parasitologically proved case of toxoplasmosis in a laboratory technician, which responded to treatment with pyrimethamine and triple sulfonamide, is described in detail. The experimental and clinical experience with treatment of toxoplasmosis is briefly reviewed. The above combined therapy is recommended for future cases of toxoplasmosis.

Summario in Interlingua

Le patiente esseva un feminin blanc assistente technic de laboratorio qui habeva laborate con toxoplasmosis experimental. Quando illa esseva admittite al hospital illa esseva acutemente malade post haber passate un periodo de circa un mense durante le qual illa habeva experientiate symptomas indefinite. Al tempore del admission le constatationes principal esseva febre, indisposition, e lymphadenopathia. Durante le prime 48 horas de observation le febre accresceva e le condition del patiente se deteriorava. Al fin de iste periodo le tractamento esseva initiate, basate super un diagnose presumptive de toxoplasmosis. In coincidentia con le tractamento il habeva un eruption cutanee. Le patiente esseva tractate con un combination de pyrimethamina (Daraprim) e un preparato de triple sulfonamidos. Le responsa al therapia esseva apparente e immediate. Le febre dispareva intra 48 horas. Altere signos objective de melioration sequeva. Le diagnose esseva confirmate parasitologicamente per le inoculation de muses con sanguine e excisos ab nodulos lymphatic. Studios serologic esseva etiam interprendite e se provava informative. Post un periodo de convalescentia prolongate sed sin incidentes le patiente esseva dimittite in stato curate.

Ultra le reporto de iste caso le autores presenta un revista del litteratura in re le tractamento de toxoplasmosis.

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ADULT TOXOPLASMOSIS: REPORT OF A CASE DUE TO LABORATORY INFECTION *

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THE accumulated records of congenital toxoplasmosis total, at the present time, several hundred cases.[1, 2, 3] On the other hand, case reports of clinical toxoplasmosis acquired after birth are few. Two cases of encephalitis in juveniles have been described, one of which terminated fatally,[4] and eight fatal cases in adults. Pinkerton and Henderson [5] reported the first two well substantiated cases. Four other fatal cases, reported by various authors, have been summarized by Kass et al.,[6] and the last two have been described by Corpening et al.[7] and by Wolf et al.,[8] respectively. Several cases of severe adult toxoplasmosis with spontaneous recovery have also been described. One of these is included in Kass's tabulation, and another was reported by Armstrong and MacMurray, who made the diagnosis by the isolation of toxoplasmas from a biopsied lymph node.[9]

The severe rickettsiosis-like form of toxoplasmosis manifested in these patients includes the following clinical features: remittent fever; a maculopapular rash sparing the scalp, palms and soles; dry, nonproductive cough; arthralgia and myalgia; myocarditis; lymphadenopathy; pneumonitis; headache; encephalomyelitis; diarrhea, and conjunctivitis. Some of these symptoms were present initially in the cases reported; others developed during the course of the disease.

There has also been described a much milder illness due to Toxoplasma infection. Siim [10] reported seven cases of this type, which he discovered serologically. Lymphadenopathy was the principal sign. Enlarged painless lymph nodes were found in the cervical and inguinal regions and in the axillae; two cases also had lymphadenopathy in the suboccipital region and in the hili of the lungs. In three patients lymph node enlargement was the only finding; one patient complained of lassitude with no obvious cause; the remaining cases showed some temperature elevation and nonspecific catarrhal symptoms. The blood picture was definitely altered, with eosinophilia up to 11.5% and lymphocytosis in two cases; in three patients the lymphocyte count was at the upper limit of normal. The lymphocytes were described as "atypical," with increased cytoplasmic basophilia. In later reports [11, 12, 13] Siim stated he had diagnosed at least 10 more such cases, had isolated toxoplasmas from the lymph node of one, and had found another case of similar nature following, but distinct from, an illness diagnosed as infectious mononucleosis.

Reports of similar mild cases of acquired toxoplasmosis have also been made by Strom,[14] Magnusson [15] and Gard and Magnusson.[16] Strom's cases showed

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only a one-day fever, with cervical lymphadenopathy; the diagnosis was based primarily on the appearance of antibodies. Magnusson reported on seven adult cases, including the one presented in more detail by Strom, of mild toxoplasmosis in adults. Most of these showed an acute febrile onset and glandular enlargement and fatigue; two patients also experienced meningo-encephalitis and myocarditis, and one showed also a maculopapular rash. In all of these cases Magnusson made the diagnosis on the basis of serology. Gard and Magnusson reported a case of the glandular form of toxoplasmosis in a woman who had just become pregnant; the first symptoms appeared about two weeks after the start of pregnancy, and the baby was normal at birth, probably because antibodies developed early enough in the mother to prevent infection of the fetus. Meira et al.[17] have reported from Brazil a similar case, in a 32 year old man. The principal symptoms were high fever, headache, asthenia, anorexia, vomiting, diarrhea, unproductive cough, nuchal rigidity, mental dullness, a maculopapular rash of the purpuric type, and lymphadenopathy. Wising [18] also reported a case of lymphadenopathy, with atypical lymphocytes, fever associated with the appearance of dye test and complement fixation test antibodies for toxoplasmosis. His case is particularly notable since a chorioretinitis appeared shortly after onset of symptoms.

The above review is not a complete summary of the described cases. Among other reports are three cases from Britain.[19] The summation of all these cases is that acquired nonfatal toxoplasmosis may be manifested by a relatively mild syndrome simulating infectious mononucleosis, as well as by more severe symptoms grading into those found in the recorded fatal cases. The following report of toxoplasmosis in a laboratory worker is presented as a further contribution to our knowledge of this human infection. Two points in regard to the present case merit attention: some previously undescribed hematologic findings, and the time of appearance of antibodies.

Case Report

Clinical History: A 36 year old white male reported to the Public Health Service Dispensary on December 26, 1951, with chief complaints of malaise, weakness, backache, headache, and intermittent chills and fever of one month's duration.

The first symptoms had appeared November 22, 1951, and consisted of shaking chills, fever to 101° F., and vomiting. There were pains in the lumbar region of the back, and aching in both sides of the upper chest radiating to both arms. There was no cough, dyspnea or stiff neck, and the patient's appetite was good. The pains, chills and fever responded completely to mild analgesics. The only persistent symptoms were fatigue and lassitude which continued until 3 weeks later, when on December 13, 1951, the fever, shaking chills and pains suddenly returned. The pains were again located in the low back and upper chest, but were also in the thighs on this occasion. Again the symptoms were relieved after analgesics and bed-rest, but the fatigue was even more marked after this attack. The third episode began December 23, 1951, 10 days later. On this date the pains returned, but there were no chills or fever. The following day the patient noted an enlarged, slightly tender gland in the left axilla. On December 25 a skin rash appeared, first on the anterior surface of the thighs, spreading on the same day to the lower legs and up to the lower abdomen. The rash consisted of flat, reddish purple areas varying in size from 1 mm. to 10 mm., with some coalescence. They did not itch and did not blanch on pressure. The

chills and fever returned on the following day when the rash was in full bloom, and the patient reported to this Clinic. The rash never appeared on the face, upper chest, back, hands, forearm or feet.

The past history revealed that the patient had worked with the parasite, *Toxoplasma gondii*, for four years. There had been only one laboratory accident when, in September, 1951, during inoculation of mice with an avirulent strain of the organism, the needle separated from the syringe. A dilute suspension of organisms was sprayed out. Calculations at the time of the accident led to an estimate that only 10 parasites reached the face, and it was presumed that immediate washing had removed these. The patient had repeatedly used his own blood as a source of accessory factor in the dye test for toxoplasmosis, and the tests were repeatedly negative. The last such use was on December 20, 1951, approximately one month after the onset of symptoms.

Admission Physical Examination: The patient was a well developed and well nourished male, looking his stated age. He appeared febrile and was sweating profusely but was calm and composed. The temperature was 100°F.; pulse rate, 100; respiratory rate, 18; blood pressure, 110/70 mm. of Hg. A walnut-sized, mildly tender lymph node was palpated in the left axilla. This was firm, movable and discrete. The posterior cervical lymph nodes were slightly enlarged bilaterally but not tender. A left epitrochlear node was enlarged to 0.5 to 1.0 cm. but was not tender. There was a purpuric rash on the lower legs, thigh and lower abdomen. The spots varied from 1 mm. to 10 mm., did not blanch on pressure, and were most marked on the lower legs. They frequently coalesced. Some enlargement of the lymphoid follicles in the pharynx was seen. The optic fundi were normal, as were the heart and lungs. The abdomen was slightly tender generally, but no organs or masses were palpated.

Course: On December 28, 1951, the patient was subjectively much improved. No new spots had appeared on the skin, and the rash had faded considerably. The temperature was 98.6°F. and had been normal for 24 hours. Pulse was 72 per minute, respiration, 18. He appeared much less toxic. The lymph nodes were slightly smaller, but small nodes were now present in the axillary and posterior cervical areas bilaterally. The lymph nodes remained tender.

By January 4, 1952, he had improved still more and had noted no further fever, chills or petechiae. The malaise was almost gone and his appetite was good. The lymph nodes were unchanged. The spleen was tender and palpable 1 to 2 cm. below the left costal margin on full inspiration.

On January 11, 1952, subjective improvement continued, but the enlarged lymph glands persisted. By January 16 the only remaining symptom was pain in the left axilla, left arm and left shoulder.

On January 21, 1952, a biopsy of the right gastrocnemius muscle was performed. Histologically it revealed no abnormalities. Mice inoculated with macerated muscle did not become infected, and subinoculations from these mice were negative through six passages.

The enlarged lymph node slowly decreased in size and was no longer palpable at the end of January, 1952.

The patient was asymptomatic, and only occasional hematologic examinations were made until March 1, 1954, when he was admitted to the Public Health Service Hospital in Baltimore, Maryland, for removal of a papilloma of the tonsil. His temperature was 99°F., blood pressure, 100/60 mm. of Hg. The liver was enlarged and was palpated 3 to 4 cm. below the right costal margin. The spleen was enlarged to 1 to 2 cm. below the left costal margin. The lymph nodes were normal. The tonsillar papilloma was removed without incident, and the patient is without symptoms at present. On reëxamination in April, 1955, the spleen and liver were no longer palpable.

Laboratory Data: Serologic tests for toxoplasmosis are given in table 1. It may be mentioned also that the serum of December 20, 1951, was used satisfactorily as accessory factor in routine dye tests for toxoplasmosis and gave readings with positive control sera essentially the same as those obtained with other accessory factor sera.

Hematologic Findings: When the patient was first seen, December 26, 1951, his white blood cell count was 4,000. Two days later it was 6,000, with 38% mature neutrophils, 7% band forms, 2% metamyelocytes, 1% myelocytes, 1% eosinophils, 36% mature lymphocytes, 4% atypical lymphocytes, and 11% monocytes. On January 2, 1952, the total count was 11,000, with 46% lymphocytes, all mature. In subsequent weekly counts during January the total white blood cells were between 8,000 and 9,000, with 45 to 50% mature lymphocytes and persistence of occasional metamyelocytes and myelocytes. The platelet counts were between 370,000 and 440,000 per cubic millimeter. Between December 28, 1951, and January 30, 1952, the sedimentation rate fell gradually from 34 mm. per hour to 10 mm. per hour, and the hematocrit rose from 38% to 45%, with a concomitant increase in hemoglobin from 13.0 to 15.8 gm., and a rise in the red blood cell count from 3,800,000 to 4,300,000. Reticulocytes numbered 3 to 5%, and there were 1 to 4 normoblasts present per 100 white blood cells from the first observation on December 28 through February 6. A bone marrow aspiration January 11 showed increased normoblastic erythropoiesis. In March, 1952, the reticulocyte level fell to 1.2%, but occasional normoblasts were still present. The percentage of lymphocytes dropped to between 30 and 40%. The presence of 1 to 4 normoblasts per 100 white blood cells persisted, however, for about two and one-half years; the hematocrit remained between 43 and 45, the reticulocyte count between 1.0 and 1.5%. At the time of the original examination the findings were interpreted as a transient leukemoid reaction with a hemolytic component. The persistence of normoblasts in the peripheral blood on subsequent examination suggested the possibility of an acquired hemolytic anemia. However, the Coombs' test was repeatedly negative. A bone marrow aspirate in March, 1954 was sparsely cellular, presumably due to dilution with peripheral blood, but the individual marrow cells were normal in morphology and distribution. No granulomatous or neoplastic process was found. Red cell survival studies were performed, using radio-chromium, in June, 1954. These showed normal survival, and hematologic examinations in early 1955 were completely normal.

TABLE 1

Results of Serologic Tests for Toxoplasmosis in the Present Case

Date of Serum Specimen	Dye Test	C. f. Test*
12/20/51	Neg.	
1/11/52	1 : 1024	4 + at 1 : 40
1/14/52	1 : 4096	4 + at 1 : 5 (q.n.s. for parallel titration)
1/22/52	1 : 2048	4 + at 1 : 80

* The complement fixation test was performed by the Section on Immunology, Laboratory of Tropical Diseases, National Microbiological Institute.

On admission the urine was alkaline and negative for albumin, sugar and bile. The sediment contained rare white blood cells and one to two red cells per high power field. Urine urobilinogen was found in a dilution of 1 : 100, and the dilution was not carried further. This level of urobilinogen was still present in the urine on January 4, 1952, and on January 11 it was positive in a dilution of 1 : 50.

Agglutinations on entry were negative for *Brucella abortus* and *Br. melitensis*, typhoid O, paratyphoid A and B, and proteus OX 19. The heterophil agglutination was negative, and typhoid H was positive, 1:80. Heterophil agglutination on January 4, 1952, was positive 1:8, but was negative with guinea pig kidney absorption.

Nonprotein nitrogen was 35 mg. per 100 ml.; thymol turbidity, 4.5 units; zinc sulfate turbidity, 11.5 units; van den Bergh, less than 0.5 mg. per 100 ml. total. Icterus index was 10 units.

Chest x-ray was negative, and an electrocardiogram was normal on January 21, 1952.

Laboratory studies during the March 1, 1954, admission to the Baltimore Public Health Service Hospital revealed a completely negative urinalysis; there was no Bence Jones protein. The VDRL test for syphilis was negative. Liver function studies were within normal limits. There was no retention of Bromsulphalein at 45 minutes. Total proteins were 6.4 gm., with albumin 4.4 and globulin 2.0 gm. One stool examination was negative for blood, ova and parasites. X-rays of the chest, skull and long bones were negative.

All bone marrow aspirates were inoculated into mice and/or chick embryos. No parasites were demonstrated.

Discussion

The appearance of the anti-Toxoplasma antibodies, demonstrable in both the dye test and the complement fixation test, is believed to be ample evidence that this was a case of toxoplasmosis.

It is noteworthy that this laboratory infection is clinically indistinguishable from the reported spontaneous adult cases. The skin rash, remittent fever, musculoskeletal aching and persistent lymphadenopathy are almost universally present. The petechial or purpuric type of skin rash was present to some degree, as in the case of Kass et al., as well as in that reported by Sexton et al.[20] and Meira et al.[17] An enlarged spleen, as in this case, has been palpated only occasionally, but toxoplasmas are usually seen in this organ at autopsy, and about one-half of the reported fatal cases have revealed lesions here.

The hematologic findings are unusual in that atypical lymphocytes, previously described in toxoplasmosis, were found only once in small numbers, while a leukemoid reaction, not previously noted, was prominent though transient. Another unusual feature is the persistence of occasional normoblasts in the peripheral blood for two and one-half years, with generally normal peripheral blood values.

The red cell survival studies performed in June, 1954, were normal, and in early 1955, three years after onset, spleen and liver as well as hematologic findings had returned to normal. Although the Coombs' test was negative throughout, the persistence of normoblasts in the peripheral blood with splenomegaly and their spontaneous disappearance support the original diagnosis of a mild hemolytic anemia. Rohn et al.[21] have reported that serum of patients with lupus erythematosus induces marked erythrophagocytosis but suppresses L. E. cell formation when incubated with the blood of patients with congenital or acquired hemolytic disease. This phenomenon was observed in the patient under discussion in 1954 but was no longer demonstrable in 1955, possibly adding additional support to the diagnosis of a hemolytic anemia.

The salient point in regard to the laboratory diagnosis is that it appears that

there was a delay in antibody production of at least four weeks. The first signs of illness appeared on November 22, and the dye test was still negative on December 20. On the latter date, 50 ml. of the patient's blood were taken for use as accessory factor serum in the dye test. There was no evidence that this specimen contained less accessory factor potency than that found in earlier samples.

The delay in appearance of antibodies may have been longer than four weeks. Unfortunately, because of misunderstanding that resulted in loss of specimens, there are no intermediate tests between December 20 and the first positive result on January 11 to furnish evidence in favor of this suspicion. However, it is believed that usually the antibodies reach an elevated titer rapidly after their initial appearance. For example, the case of Sexton et al. showed a dye test titer of 1 : 256 only four days after the first positive titer of 1 : 16 was obtained.

Gard and Magnusson [16] took note, in their case study of toxoplasmosis early in pregnancy, of the late appearance of antibodies. The titer was only 1 : 50 three months after onset, rose to 1 : 2,000 and 1 : 4,000 two and three months later, and was still high after one year. They admit that it is not possible unequivocally to relate the glandular disease with these late-appearing antibodies, but argue correctly that the delayed serologic reaction does not serve as decisive evidence against such a relation. One might add that, were toxoplasmosis acquired later in the pregnancy, which would be the logical assumption if the serologic response were considered to be more rapid, then it would be even more peculiar that the fetus was not infected.

There is one other point to be made in the case of Sexton et al.: The history revealed a period of somnolence, lassitude and fatigue which lasted for several months before the acute onset. While there is, admittedly, no way to demonstrate that these symptoms were related to the infection, it is considered worth while to emphasize that the appearance of antibodies may have been delayed for some time and not in reality have been so rapid in appearance as their presence on the fourth day of the acute disease would indicate. As to the possibility of a long incubation period in some cases, it is well to point out also that in the present case the only laboratory accident occurred about two months before the appearance of symptoms and about three and one-half months before the first positive serum. Even after 28 days of symptoms the dye test was still negative, becoming positive between the twenty-eighth and fiftieth day. Kass et al. also found the antibodies slow in appearing; in their case the dye test was negative on the second hospital day, which was 12 to 14 days after onset of illness; the next test, strongly positive, was done on serum taken on the thirty-sixth hospital day.

It is believed, therefore, that the appearance of antibodies in cases of acquired toxoplasmosis may be delayed considerably beyond the time of onset of illness. Although this point has not been unequivocally established by the observations recorded above, it is certainly indicated. On the basis of this thesis, it would be profitable to investigate further such problems as the relation of toxoplasma to cases of spontaneous abortion, with serologic tests performed at, say, the sixth week rather than earlier. Furthermore, study of unexplained cases of "glandular fevers" might well be extended beyond the time of remission. It is to be noted that in the present case the patient was much improved at the time antibodies were demonstrated.

Summary

A case of the "glandular" form of toxoplasmosis acquired by laboratory infection is described. The main features of interest were evidences of a mild hemolytic anemia associated with splenomegaly, and late appearance of antibodies revealed by the dye test.

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Summario in Interlingua

Es describite un caso de toxoplasmosis resultante ab un infection accidental al laboratorio. Le patiente esseva un masculo blanc de 36 annos de etate con un historia de indisposition, debilitate, fatiga, e attaccos intermittente de frigido febril, accompaniate de mal de capite e dolores thoracic e dorsal, radiante verso le extremitates, de un durantia de un mense. In le axilla sinistre il habeva un grande nodo lymphatic de sensibilitate sub pression, e eruption cutanee esseva presente al femore anterior, le gambas inferior, e le abdomine. Plus tarde, nodos cervical e epitrochlear se allargava, ben que le patiente esseva subjectivemente meliorate un septimana post su presentation. Le examine laboratorial monstrava un leucopenia initial de breve durantia, sequite per un retorno a contos normal (con un relative lymphocytosis de 45 a 50 pro cento de lymphocytos matur e persistentia de sporadic myelocytos e metamyelocytos). Atypic lymphocytos esseva observate solmente un vice. Le sedimentation se relentava ab 34 a 10 mm per hora in le curso de un mense de observation. Le hematocrite monstrava durante le mesme periodo un elevation ab 38 a 45 pro cento, accompaniate de un augmento de hemoglobina ab 13,0 a 15,8 g e un augmento del conto erythrocytic ab 3.800.000 a 4.300.000. Le conto del plachettas esseva elevate, e le examine de medulla ossee revelava un augmentate erythropoiese. Le presentia de inter 1 e 4 normoblastos per 100 leucocytos persisteva durante circa duo annos e medie, con un conto reticulocytic inter 1,0 e 1,5 pro cento. Le hepate e le splen se allargava. Durante al minus duo annos, le hepate esseva palpabile 3 a 4 cm infra le margine costal e le splen 1 a 2 cm infra ille margine. Post un mense le nodos lymphatic esseva devenite inpalpabile. Tres annos e medie post le morbo initial, studios del superviventia de cellulas sanguinee esseva normal. Roentgenogrammas thoracic e electrocardiogrammas esseva normal. Le diagnose esseva facite per le demonstration, septe septimanas post le declaration del symptomas, de titros de 1:1024 e 1:40 pro anticorpores in le test a coloration e le test a fixation de complemento, respectivemente. A quatro septimanas post le declaration del symptomas le mesme tests habeva essite negative. Post octo septimanas illos accresceva a 1:4096 e 1:80, respectivemente.

Nos signala que iste caso de infection laboratorial esseva clinicamente indistinguibile ab reportate spontanee casos adulte. Tractos prominente esseva le reaction leucemioide e le persistente allargamento de hepate e splen, insimul con le persistentia (e disparition simultanee) de normoblastos sporadic in le sanguine peripheric. Le apparition de anticorpores esseva retardate. Nulle anticorpores esseva demonstrabile un mense post le declaration del symptomas. Le sol traciabile accidente laboratorial habeva occurrite con un relativemente avirulente racia de toxoplasma a un periodo duo menses ante le symptomas initial e al minus tres menses o plus ante le apparition de anticorpores.

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UNSUSPECTED PHEOCHROMOCYTOMA RESULTING IN POSTOPERATIVE DEATH *

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Because of prolonged life span an increasing number of elderly patients with hypertension is being subjected to various types of surgical procedures. It is therefore important to remember that lethal hypertensive crises from unsuspected pheochromocytomas may be precipitated by the trauma of anesthesia and surgery.

In a recent review of the literature by Apgar and Papper,[1] it was disclosed that the operative mortality in patients on whom surgery was performed without prior knowledge of the presence of pheochromocytoma was 50%. Fifteen of the 16 patients who died did so within two to 48 hours postoperatively, in irreversible circulatory collapse. A similar case in a 68 year old patient who died immediately following an exploratory laparotomy, and in whom the postmortem diagnosis was clinically occult bilateral pheochromocytoma, is presented.

Case Report

A 68 year old white male was admitted to the hospital for diagnosis of an upper abdominal mass which had been present for three months. The mass had first been noted after two short episodes of fever, abdominal pain, and nausea and vomiting for which he was treated in other hospitals. On one of these occasions his temperature was 101° F. Several urinalyses revealed intermittent albuminuria and intermittent trace glycosuria.

Past medical history included blood pressure recordings varying from 150 to 164 mm. of mercury systolic, and 90 to 90 mm. of mercury diastolic at times during 1952. During a hospital admission for left flank pain in 1951, blood pressure was 160/116 mm. of mercury; chest x-ray, blood chemistry and urine examinations at that time were within normal limits; one week prior to this admission blood pressure was recorded as 220/124 mm. of Hg.

In 1932 the patient had been hospitalized for pain in his right lumbar area; microscopic hematuria was present. At cystoscopy the examiner was unable to catheterize the right ureter; pyelography suggested the presence of a probable calculus in the right renal pelvis. Blood pressure during this admission was 130/88 mm. of mercury. In 1918 a herniorrhaphy and excision of a right paratesticular mass was performed; more specific details of this illness are unavailable.

Physical examination on his admission to the Delaware Hospital revealed a blood pressure of 166/96 mm. of mercury. The remainder of the physical examination was negative except for a lemon-sized mass in the left upper abdominal quadrant which was freely movable and which seemed to pulsate slightly.

Laboratory data included: hemoglobin, 14.9 gm.; normal total and differential leukocyte count; blood urea nitrogen, 5 mg.%; fasting blood sugar, 135 mg.%; serum amylase, 24 units; phenolsulfonphthalein excretion of 20% in 15 minutes, and 38% total in 120 minutes. Urinalysis demonstrated no albuminuria or glycosuria; specific gravity was 1.022. Electrocardiogram was interpreted as showing a left axis shift. Barium enema, upper gastrointestinal series and aortogram revealed no abnormalities.

The patient was felt to be a benign essential hypertensive, presenting no special operative risk, and laparotomy for diagnosis was elected. He received preoperative

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sedation of Demerol, 75 mg., and scopolamine, 0.3 mg. Anesthesia was induced with 2% Surital (thiamylal), and maintained with nitrous oxide and cyclopropane. A continuous drip of 0.05% succinyl choline was used to facilitate relaxation. The surgical procedure, which required 50 minutes, demonstrated a well circumscribed, fatty appearing tumor of the mesentery, which was biopsied. At the beginning of the procedure the patient's blood pressure was 180/100 mm. of mercury; during surgery it gradually rose to a level of 230/130 mm. of mercury. Pulse rate was not recorded. Spontaneous respirations were sufficiently depressed to require assistance throughout the procedure; respiratory rate was maintained at 20 per minute.

At the close of the operation it was noted that the patient's color was poor. He was transferred from the operating room to the anesthesia recovery room. His cyanotic color deepened, and within 15 minutes his blood pressure fell precipitously to an unrecordable level, at which time he developed acute fulminant pulmonary edema. An endotracheal tube was inserted, following which spontaneous respiratory activity ceased. Continuous positive pressure respiration was instituted and maintained for two hours, at the end of which time he was pronounced dead. During this period the patient received oxygen with vaporized 95% ethyl alcohol. An unsuccessful attempt at phlebotomy was made, and Digalen, 2 c.c., containing 1 USP unit, and caffeine and sodium benzoate, 2 c.c., containing 0.5 gm., were administered intravenously.

At postmortem examination * the heart weighed 575 gm. There were moderate left ventricular hypertrophy and dilatation of the right chambers. The aorta demonstrated atherosclerotic plaques throughout its extent. Both lower lobes of the lungs were congested, and on cut section exuded large amounts of pink fluid. There was a mesenteric lipoma, 12 cm. in diameter, which contained areas of fat necrosis. The adrenals were described as follows: "The adrenal on the right side is globular; it measures 3.5 cm. in diameter. On cut section, the distortion appears to be due to a cyst with a smooth inner wall, containing clear amber fluid. However, the wall of the cyst is composed of tissue which is reddish gray in color, and appears to be tumorous in nature. This is surrounded at its periphery by a margin of adrenal cortex. At one extremity, the adrenal gland is visible as an extremely hypoplastic structure, with the cyst invading the medullary area. The left adrenal shows medullary involvement. On cut section, the medulla is covered with a reddish gray, soft, tumor-like tissue, measuring approximately 1.0 cm. in diameter. The cortex, as a result, is thin at its periphery."

Histologically, both adrenal tumors were pheochromocytomas.

Comment

As pheochromocytoma represents one of the few causes of hypertension for which therapy in the form of extirpation of the adrenal medullary tumor offers cure, clinicians in the past decade have become increasingly alerted to the necessity for considering pheochromocytoma, not only in the presence of the originally described syndrome of paroxysmal hypertensive and hypermetabolic crises, but also in all patients with blood pressure levels above normal.[2] It has been repeatedly emphasized in the past few years that 70% of patients with pheochromocytoma have a sustained hypertension which is clinically in no way different from essential hypertension.[3, 4] Wells and Bowman, as early as 1937, stated that all patients with functioning pheochromocytomas will progress to chronic hypertension if they live long enough.[5] Thirty-seven of the 50 cases

* Autopsy performed by Dr. John W. Howard and Dr. Park W. Huntington, Jr.

reviewed by Green in 1946 were chronically hypertensive;[4] 18 of 32 patients of a series studied by Goldenberg et al. had persistent hypertension.[2]

A recent editorial in the *Annals of Internal Medicine* emphasizes that pharmacologic tests are the cornerstone of diagnosis of pheochromocytoma, and that phentolamine (Regitine) is a simple, safe testing agent which will usually lower blood pressure in patients whose hypertension is due to pheochromocytoma.[3] In light of the high incidence of hypertension in elderly people, it is suggested that testing with phentolamine be performed in all hypertensive patients, irrespective of age, before subjecting them to surgery. Otherwise, the stimulation to the adrenal medullary tumor may precipitate cardiac arrhythmias or peripheral vascular collapse secondary to markedly increased peripheral arteriolar resistance, with subsequent pulmonary edema.

Summary

1. Pheochromocytoma may be the cause of sudden death during or immediately after unrelated surgery.

2. The importance of the constant recognition that hypertension resulting from pheochromocytoma may in all ways resemble essential hypertension is reëmphasized.

3. A case is presented of pulmonary edema and circulatory collapse resulting in death in a 68 year old man subjected to laparotomy, in whom bilateral pheochromocytomas were demonstrated at necropsy.

Summario in Interlingua

A causa del crescente duration del vita un crescente numero de hypertensive patientes de etates avantiate es subjicite a interventiones chirurgic. Proque le mortalitate operative inter patientes con non-suspicionate pheochromocytoma es 50 pro cento, il es importante rememorar se que crises letal ab non-suspicionate pheochromocytoma pote esser precipitate per le trauma de anesthesia e chirurgia.

Le hypertension que resulta de pheochromocytoma resimila hypertension essential in omne aspectos in possibilemente 70 pro cento del casos. Tests diagnostic a phentolamina (Regitina) deberea esser executate in omne patientes hypertensive ante que le intervention chirurgic es initiate.

Es presentate un caso de edema pulmonar con collapso circulatori que resultava in le morte del patiente. Il se tractava de un homine de 68 annos de etate qui esseva subjicite a laporotomia. Non-suspicionate pheochromocytomas bilatere esseva demonstrate al necropsia.

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3. Editorial: The diagnosis of pheochromocytoma, Ann. Int. Med. **39**: 1333, 1953.
4. Green, D. M.: Pheochromocytoma and chronic hypertension, J. A. M. A. 131: 1260, 1946.
5. Wells, A. H., and Bowman, P. G.: The clinical and pathological identity of pheochromocytoma, J. A. M. A. **109**: 1176, 1937.

GLYCINE AND SODIUM GLUCURONATE IN THE MANAGEMENT OF CONVULSIONS DUE TO HYDRAZIDES *

By Sol Katz, M.D., F.A.C.P., Abe Gimble, M.D., Georges McCormick, M.D., and Benjamin Prescott, Ph.D., *Washington, D. C.*

Isoniazid and Salizid (Compound 1595,† also a hydrazide derivative of isonicotinic acid) are two of the most effective and least toxic antituberculous drugs presently available. Although significant side effects are infrequent from the use of these drugs, peripheral neuritis and convulsions constitute toxic reactions sufficiently severe to require that therapy be discontinued or dosage reduced.

Isoniazid, in therapeutic doses, may produce convulsions which resemble grand mal epilepsy.[1] This problem may occur in patients without a previous history of epilepsy. The hazards of isoniazid therapy in epileptics have been reported by Fetterhoff,[2] who cited a case of status epilepticus precipitated by isoniazid. The tuberculous patient with epilepsy requires a higher maintenance dose of anticonvulsant medication during isoniazid therapy.

Salizid has been found to be less toxic than isoniazid, and frequently can be used in patients who have developed isoniazid neuritis or "toxic encephalopathy." [3] However, Salizid, especially in large doses, may occasionally cause peripheral neuritis and convulsions.

Hydrazide-induced seizures can be controlled by depressant drugs. It has been suggested that pyridoxine will prevent isoniazid-induced seizures.[4] It has been found, however, that the ability of pyridoxine to prevent isoniazid-induced convulsions is not constant, and in most instances therapy must be supplemented with such anticonvulsant drugs as the barbiturates.

Prescott and his associates have shown that two well known detoxifying agents, glycine and sodium glucuronate, administered simultaneously with isoniazid in mice, have a marked effect in increasing tolerance to this drug.[5] The introduction of supplementary quantities of these two chemicals, both of which are normally available in the body, permits mice to survive an amount of isoniazid some five times larger than the otherwise toxic dose. The same authors have also shown that these compounds do not lower the blood plasma concentrations of isoniazid, thus indicating that they have no effect on the excretion of isoniazid. Furthermore, these detoxifying substances do not antagonize the bacteriostatic action of isoniazid "in vitro."

In another report [6] it was shown that mice experimentally infected with human tubercle bacilli, when treated with glycine and sodium glucuronate in combination with large doses of isoniazid (500 mg./kg.) could be kept on continued therapy over a longer period of time (over 200 days) than was previously possible with large doses of isoniazid alone. Furthermore, following the administration of the higher doses of isoniazid in combination with glycine and sodium glucuronate, they observed eradication of tubercle bacilli in many of the animals.

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† Supplied by Dr. George Mast, Nepera Chemical Company, Yonkers, N. Y.

Such experiments showed that the two detoxifying chemicals had no inhibitory effect on the chemotherapeutic activity of isoniazid.

We have also used glycine and sodium glucuronate in patients with isoniazid neuritis. Isoniazid was continued in these patients and, although ineffective in the management of neuritis, glycine and sodium glucuronate did not interfere with the continued therapeutic antituberculous activity of isoniazid.

Gatalone, an isonicotinyl hydrazide of glucuronolactone, has been reported by American [7] and French [8] writers to possess the same antituberculous activity as does isoniazid. Gatalone is well tolerated and does not cause toxic reactions in a dose five times greater than that of isoniazid. It may be postulated that Gatalone is very quickly broken up into isoniazid and glucuronolactone, and that the freed glucuronolactone acts as a powerful detoxifying agent of isoniazid.

Glycine and sodium glucuronate have been reported to prevent isoniazid-induced convulsions in mice.[5] It therefore seemed desirable to ascertain if they were similarly effective in man.

Case Reports

Case 1. A 59 year old Negro with pleural effusion was admitted to District of Columbia General Hospital on February 19, 1954. Antituberculous therapy was started on April 24, 1954. This regimen consisted of streptomycin, 1 gm. twice weekly, PAS, 12 gm. daily, and isoniazid, 400 mg. daily. The patient showed rapid improvement both subjectively and objectively. On August 19, 1954, after four months of therapy, the patient became disoriented, with incoherent mumbling. Suddenly a generalized convulsion occurred. Lumbar puncture gave normal findings, including a culture negative for tubercle bacilli. Convulsions recurred, and he remained stuporous. Neurologic examination was negative. Phenobarbital was given intravenously and intramuscularly. Isoniazid was discontinued. The seizures subsided the same day except for intermittent muscular twitching, which continued for 24 hours. During the succeeding days the patient became more alert and returned to his preconvulsive state. There were no more seizures.

Anticonvulsive therapy was discontinued on August 23, 1954. On September 21, 1954, isoniazid, 400 mg. daily, was started again. On September 24, 1954, the patient again developed generalized convulsions. A lumbar tap again revealed normal findings. Anticonvulsive therapy was started again and isoniazid was discontinued. The seizures subsided and anticonvulsive therapy was discontinued on September 26, 1954. On October 23, 1954, isoniazid was started again but in conjunction with glycine, 4 gm., and sodium glucuronate, 4 gm. daily. On this regimen there have been no more convulsions. Electroencephalograms made while the patient was not receiving isoniazid, as well as during the period in which convulsions were controlled while he was on isoniazid, showed abnormality suggesting diffuse brain damage.

Case 2. A 19 year old deaf-mute Negro with far advanced pulmonary tuberculosis was admitted to the District of Columbia General Hospital on July 6, 1953. The patient had been having epileptic seizures since the age of seven. Medical treatment for his epileptic condition had been started in 1946. This treatment consisted of Dilantin, 0.1 gm. three times a day, and phenobarbital, 30 mg. three times a day. The seizures diminished in frequency, occurring approximately once or twice a month.

Antituberculous therapy was started July 11, 1953, shortly after his admission to the hospital; this consisted of oxytetracycline, 1 gm. daily, and isoniazid, 200 mg. twice a day. Dilantin and phenobarbital were continued as before. After about three months of therapy it was noted that the epileptic seizures were increasing in frequency. Isoniazid was therefore discontinued on October 9, 1953, and Salizid was started in doses of 250 mg. twice a day. Although the frequency of the seizures

decreased somewhat, the patient continued to have four or five seizures a month. In addition, it was necessary at frequent intervals to discontinue Salizid for five-day periods to avoid the danger of status epilepticus. With the addition of glycine, 4 gm. daily, and sodium glucuronate, 4 gm. daily, the frequency of the seizures diminished to one or two a month. At no time was it necessary to discontinue Salizid.

Summary

In two patients with convulsions induced by isoniazid and Salizid, the concomitant use of glycine and sodium glucuronate prevented the occurrence of convulsions, thereby permitting continued use of the antituberculous agents.

Summario in Interlingua

Isoniazido e Salizido (iste ultime etiam un hydrazido derivate ab acido isonicotinic), ben que illos es efficacissime agentes antituberculotic, produce a vices convulsiones simile al epileptic grande mal. Glycina e glucuronato de natrium, duo ben-cognoscite agentes distoxificante, ha un marcate effecto de augmentar le toleration de muses pro isoniazido; illos rende le muses capace a superviver a cinque vices le dose que es usualmente letal. Glycina e glucuronato de natrium etiam preveni convulsiones isoniazidogene in muses. Le duo compositos non reduce le concentration de isoniazido in le plasma sanguinee. Illos etiam ha nulle effecto super le action bacteriostatic exercite per isoniazido in vitro super bacillos tuberculotic human.

Post le establimento experimental de iste facto il pareva desirabile investigar si glycina e glucuronato de natrium es similemente efficace in le prevention de convulsiones hydrazidogene in humanos. Per consequente, duo patientes con convulsiones precipitate per Salizido e isoniazido esseva tractate con 4 g de glycina e 4 g de glucuronato de natrium per die, insimul con le previemente toxic dose del hydrazido. Le convulsiones esseva prevenite e le continuate uso del efficace hydrazido deveniva possibile.

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EDITORIAL

ASSOCIATION OF IRRADIATION WITH NEOPLASIA IN CHILDREN AND ADOLESCENTS

SINCE Friedlander [1] irradiated the enlarged thymus gland of an infant with status lymphaticus in 1907 with excellent symptomatic improvement, irradiation of enlarged thymus glands has been a common practice in this country, particularly between 1930 and 1950. Recently, reports have begun to stress the occurrence of malignancy in those children and adolescents who have had radiation for thymic enlargement and other benign conditions during infancy and early childhood.[2, 3, 4, 5]

Radiation as a possible etiologic factor in carcinoma of the thyroid gland in children and adolescents was first suggested by Duffy and Fitzgerald [2] in 1950. In a series of 430 cases of cancer of the thyroid at Memorial Hospital between 1932 and 1948, 28 occurred in patients under 18 years of age, an incidence of 6.5%. Ten of these 28 young patients had been subjected to short courses of irradiation for enlarged thymus glands between the fourth and sixteenth months of life. At the time of occurrence of the thyroid carcinoma, these patients ranged from 4 to 18 years of age.

Simpson, Hempelmann and Fuller [3] studied the frequency of neoplasia in 1,722 children who had received radiation to the thymus gland between 1926 and 1951. Most of these patients were treated when only a few weeks of age but a few were as much as one year old. In most instances the dose of irradiation was very small, but 42% of the patients received a dose exceeding 200 roentgens, measured in air. They were able to collect data on 1,400 of these children, 81% of the total treated, and found that 17, and possibly 19, of them developed some type of malignancy. In the 17 cases of malignancy there were seven patients with leukemia and six with thyroid carcinoma. The incidence of each of these is significantly higher than that found in untreated siblings or the general population. The incidence of thyroid adenoma and exostosis in this series is also probably higher than normal.

Recently, Clark [4] reported 13 cases of thyroid carcinoma in children and adolescents under 15 years of age. All of these patients had been subjected to previous irradiation, between the ages of two months and six years, to the upper chest, for an enlarged thymus or pertussis, or to the head and

[1] Friedlander, A.: Status lymphaticus and enlargement of the thymus with a report of a case successfully treated by the x-ray, Arch. Pediat. **24**: 409, 1907.

[2] Duffy, B. J., and Fitzgerald, P. J.: Thyroid cancer in childhood and adolescence. Report of twenty-eight cases, Cancer **3**: 1018, 1950.

[3] Simpson, C. L., Hempelmann, L. H., and Fuller, L. M.: Neoplasia in children treated with x-rays in infancy for thymic enlargement, Radiology **64**: 840, 1955.

[4] Clark, D. E.: Association of irradiation with cancer of the thyroid in children and adolescents, J. A. M. A. **159**: 1007, 1955.

[5] Dameshek, W.: The outlook for the eventual control of leukemia, New England J. Med. **250**: 131, 1954.

neck area for cervical adenitis, enlarged tonsils, adenoid tissue or sinusitis. The total dose ranged from 200 to 725 roentgens, measured in air, in divided doses. The ages varied from 4 to 15 years, at the time of the histological diagnosis of these tumors, with an average interval of 6.9 years between the time of irradiation and the diagnosis of neoplasm.

Warren, Alvizouri and Colcock [6] reported upon 23 cases of thyroid carcinoma in patients under 20 years of age. Only one patient in this group had received radiation to the thymus gland prior to the development of the malignancy. They did not mention the use of previous radiation about the head and neck, and apparently this series of patients was not investigated from this standpoint.

Between 1937 and 1946 Conti and Patton [7] studied a series of 7,400 consecutive newborn infants. Of these infants, 3 to 4% were found to have roentgen evidence of thymic enlargement and, early in the study, were given roentgen therapy, regardless of the presence or absence of symptoms. Later, for no apparent reason, all of these newborns received small doses of radiation, but later this was discontinued. Follow-up studies were incomplete, but no evidence of neoplasm was noted.

Although still relatively infrequent, the incidence of carcinoma of the thyroid gland in children and adolescents is increasing. The recently reported high incidences of previous roentgen therapy to the thymus gland and benign lesions of the head and neck in infants, who subsequently develop thyroid cancer, strongly suggest an association between thyroid cancer in childhood and adolescence and prior irradiation. Simpson and his associates [3] even suggested that a correlation exists between the form of treatment and subsequent development of thyroid malignancy, as all six of their cases occurred in a group of 804 patients who received more than 200 roentgens of radiation and none in the group of 604 patients who received less. All of Clark's [4] cases received a total of 200 roentgens or more. While it is stated that all of these patients received a total of 200 roentgens or more, it is quite probable that the thyroid gland in most instances received much less, as it was on the edge of the treatment field where there is a marked drop in the dosage.

Doniach [8] has shown that radiation will produce cancer of the thyroid gland in animals, but this has not been substantiated in adult human beings. Quimby and Werner,[9] in a survey of 70 radiologists and 31 thyroid specialists, could find no evidence to indicate late malignant changes in the thyroid gland following roentgen therapy for hyperthyroidism. Likewise,

[6] Warren, S., Alvizouri, M., and Colcock, B. P.: Carcinoma of the thyroid in children and adolescents, Cancer **6**: 1139, 1953.

[7] Conti, E. A., and Patton, G. D.: Study of the thymus in 7,400 consecutive newborn infants, Am. J. Obst. and Gynec. **56**: 884, 1948.

[8] Doniach, I.: The effect of radioactive iodine alone and in combination with methylthiouracil upon tumor production in the rat's thyroid gland, Brit. J. Cancer **7**: 181, 1953.

[9] Quimby, E. H., and Werner, S. C.: Late radiation effects in roentgen therapy for hyperthyroidism. Possible bearing on the use of radioactive iodine, J. A. M. A. **140**: 1046, 1949.

they could find no incidences of thyroid carcinoma following roentgen therapy to other conditions, such as carcinoma of the larynx, where the thyroid receives a far greater dose of radiation than in the treatment of hyperthyroidism.

Dailey, Lindsay and Miller [10] found histologic evidence of Hashimoto's thyroiditis in 39% of the thyroid glands following treatment of hyperthyroidism with radioactive iodine, as compared to 3% in those glands prepared for surgery by conventional methods. They concluded that the Hashimoto's thyroiditis is directly the result of irradiation from the radioactive iodine on the hyperplastic thyroid gland. Norris and Pollock [11] believe that there is a significant relationship between Hashimoto's thyroiditis and thyroid malignancy, as in one series of cases, malignant neoplasms were four times greater in glands with some degree of Hashimoto's thyroiditis than in those without it. This would tend to indicate a rather marked increased incidence of malignancy developing in those thyroid glands previously subjected to radioactive iodine therapy. Thus far, this supposition has not proved to be correct, though maybe sufficient time has not elapsed for the development of late malignant changes.

If small or moderate doses of irradiation to the adult thyroid gland are not carcinogenic, one wonders why there would be any association between thyroid cancer in children and adolescents and prior radiation, unless the thyroid cells of a newborn or infant are more susceptible than those of an adult. A hormonal factor may be involved as the thymus-thyroid and thymus-pituitary axes are not clearly understood.[12] Doniach [8] suggested that radiation produces irreversible cell changes in the thyroid gland rendering them more liable to tumor formation when stimulated to undergo hyperplasia by prolonged thyrotropic stimulation following interference with thyroxine synthesis.

The incidence of leukemia has risen from a rate of 2.1/100,000 in 1930 to 5.5/100,000 in 1949.[13] This increased incidence correlates closely with the increased use of all types of radiation. The leukemogenic action of x-rays has been well documented from both clinical and experimental observations.[14, 15, 16, 17, 18] However, the relationship of such small doses of

[10] Dailey, M. E., Lindsay, S., and Miller, E. R.: Histologic lesions in thyroid gland of patients receiving radioiodine for hyperthyroidism, J. Clin. Endocrinol. **13**: 1513, 1953.

[11] Norris, W. J., and Pollock, W. F.: Nodular goiters in children, Am. J. Surg. **90**: 345, 1955.

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[16] Kaplan, H. S., and Brown, M. B.: Protection against radiation induced lymphoma development by shielding and partial-body irradiation of mice, Cancer Res. **12**: 441, 1952.

[17] Folley, J. H., Borges, W., and Yamawaki, T.: Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan, Am. J. Med. **13**: 311, 1952.

[18] Nagareda, C. S., and Kaplan, H. S.: The effect of hypophysectomy and x-irradiation on lymphoid organs and on the induction of lymphoid tumors in C57BL mice, J. Nat. Cancer Inst. **16**: 139, 1955.

radiation, as received during irradiation of a thymus or benign lesions of the head and neck, to the subsequent development of leukemia is only speculative. Dameshek [5] commented that on one occasion several years ago he observed, within a period of one month, three children with leukemia who had been given roentgen therapy for thymic hyperplasia. Only Simpson et al.[3] presented statistics of an increased incidence of leukemia in children and adolescents following irradiation of the enlarged thymus gland, but they could find no definite relationship between the type or dose of radiation and the subsequent development of leukemia, as in their cases of thyroid cancer.

With the apparent increasing incidence of thyroid carcinoma and leukemia associated with increased irradiation of benign lesions of the head and neck and chest, one wonders what percentage of infants have been treated unnecessarily for thymic enlargement when it was asymptomatic or did not actually exist. The roentgen diagnosis of thymic enlargement is unsatisfactory because no standard of normal limits has been established for various ages and because the width of the mediastinal soft tissues varies in the same infant under different conditions, such as the respiratory phase, cardiac phase and position of the patient. Upon reviewing the films of many cases of "enlarged thymus" before or after therapy, one concludes that most of the so-called enlarged thymus glands are simply a widened mediastinum or prominent thymus due to the expiratory phase of the film. The widened mediastinum will narrow or the "enlarged thymus" disappear when a good inspiratory film is obtained. Most pediatricians and radiologists now believe that the thymus gland seldom, if ever, produces respiratory embarrassment or other symptoms.

With the increased use of extensive roentgen diagnostic procedures during the past few years, some may wonder if there will be an increased evidence of neoplasia in those infants, who have been subjected to these extensive diagnostic procedures, such as cardiac catheterization and angiocardiography. This seems unlikely as the doses of radiation are usually small and the procedures not repeated at close intervals.[10] However, only time will tell the complete story.

Even though the reported high incidence of association between irradiation in infants and childhood and the subsequent development of malignancy in childhood and adolescence is striking and cannot be denied, the evidence is not conclusive. Duffy and Fitzgerald [2] and Clark [4] have analyzed only a few cases of thyroid carcinoma in children and adolescents and found the incidence of previous irradiation to be high. This may be misleading. A more valid and realistic approach would be to analyze a large number of patients who had received small doses of radiation during infancy, as did

[10] Dubilier, W., Burnett, H. W., Dotter, C. T., and Steinberg, I.: Radiation hazard during angiocardiography, Am. J. Roentgenol. 70: 441, 1953.

Simpson et al.,[3] and determine the incidence of neoplasia in this group, as compared with the general population. While the report of Simpson et al.[3] indicates an increased incidence of neoplasia following irradiation in infancy and early childhood, their 17 cases are too few to be conclusive. Analysis of many more patients is necessary before any definite conclusions can be drawn. Until that time, ionizing radiations should be reserved, with a few exceptions, for treatment of malignant conditions.

JOHN M. DENNIS, M.D.

REVIEWS

Introduction to Virology. By GILBERT DALLDORF, M.D. 102 pages; 15.5 × 23.5 cm. Charles C Thomas, Springfield. 1955. Price, $3.50.

Technics for the study of viruses have improved greatly in recent years. New groups of viral agents are being recovered from man at an unprecedented rate, many still awaiting assessment of their place in human disease. "New" clinical entities with specific causative agents are being segregated from the perplexing mass of fever of unknown origin. Most of this is being done by virus laboratories with more or less special interests. Except in rather rare instances, however, the practitioner of medicine has little access to diagnostic facilities of a routine nature for viral diseases. Paradoxically, at a time when newly recognized entities are being described in his professional journals, he is left at the bedside to speculate as best he can about the nature of the disease which he has been called in to treat.

The thesis set forth in the preface of this small volume by Dr. Dalldorf is based on his conviction that the hospital laboratory ought to be able to perform many of the virus diagnostic procedures. His purpose is to stimulate interest of bacteriologists, pathologists, and others in hospital virology, hoping to encourage some to develop virology as a regular part of the hospital laboratory facility. The author attempts to dispell the myth that virological procedures are too complicated to be performed at the hospital laboratory level.

The book, based on a series of lectures given to students at the School of Medicine, University of Buffalo, is a readable summary of current information on the more common viral diseases of man encountered in the United States. The last two chapters discuss briefly the design of a virus laboratory and some of the more common technics, respectively. Indeed, it would be profitable reading for persons who are not familiar with the subject but who would like a brief orientation into the field of medical virology by a simple, clear and current summary of a general nature. It is intended as an introduction. With few exceptions, it is written without the benefit of a bibliography and is not sufficiently comprehensive to serve as a clinical guide or a laboratory manual.

CHARLES L. WISSEMAN, JR., M.D.

Fluid and Electrolytes in Practice. By HARRY STATLAND, M.D. 206 pages; 24 × 15.5 cm. J. B. Lippincott Company, Philadelphia. 1954. Price, $5.00.

This little book is probably the best so far to appear from the point of view of the doctor or student who requires a simple and essentially practical guide through the wilderness of electrolyte balance and imbalance. According to the author's preface, the material was originally presented at the University of Kansas as a series of lectures for undergraduate and postgraduate students; at the request of many of these, the lecture notes were assembled and amplified into this very practical text.

The book is divided into two parts. Part 1 is devoted to general principles—fluid structure (an excellent opening chapter); movements of fluids in the body; intake and output; prevention of imbalance in the postoperative patient; water depletion; salt depletion; mixed depletions; potassium and magnesium; acid-base balance; treatment of the depletions; edema, diuretics and water intoxication. The chapter on acid-base balance is a particularly good exposition of a notably difficult subject.

In Part 2 the author effectively applies the principles enunciated in Part 1 to special situations—heart failure; renal and urological diseases; diabetic acidosis; pediatric fluid balance; burns; cirrhosis; toxemia of pregnancy. The volume is completed by a bibliography of 161 well selected references.

Criticisms are minor. Some sections are not as lucid or as detailed as they might be; for instance, after digesting the admirable accounts of fluid shifts in pure water and pure salt depletion, one is disappointed to find only an abbreviated and unsatisfying description of the shifts in a mixed depletion—the commonest type encountered in practice. Again, the simple and helpful drawings depicting the two fluid compartments would be even more valuable if the compartments were represented more nearly their actual relative proportions. For example, from figure 15, which illustrates the state of the compartments in mixed depletions, one would conclude that considerably more fluid is lost from the extracellular than from the intracellular compartment, though the text tells us that approximately equal amounts are lost from each. This inconsistency is due to the fact that in this and indeed in all the drawings representing the two compartments side by side, the extracellular appears to have about two thirds the capacity of the intracellular instead of about one half.

For the most part, however, the text is clearly written and readily understood and is aided by clear and simple diagrams. This is not an exhaustive treatise on the subject, but it will answer most of the common practical questions that arise in the course of fluid and electrolyte administration in hospital practice.

H. J. L. M.

Fluoroscopy in Diagnostic Roentgenology. By Otto Deutschberger, M.D., Assistant Clinical Professor of Radiology, New York Medical College, Roentgenologist in charge, Bird S. Coler Memorial Hospital, N. Y., Associate Visiting Roentgenologist, Metropolitan Hospital, N. Y. 771 pages; 18 × 26 cm. W. B. Saunders Company, Philadelphia. 1955. Price, $22.00.

Fluoroscopy in Diagnostic Roentgenology is a complete and accurate presentation of the subject of fluoroscopy, filling a previous gap in diagnostic roentgenology. It deals with the entire scope of fluoroscopy, including not only its great potential, but also its limitations.

The book is written in two parts. Part I is a general description of fluoroscopy including historical factors, equipment and the physics and hazards of this method. Part II deals with fluoroscopy of specific organs and anatomic tracts with emphasis on the physiologic rather than the usual anatomic aspects. The possibilities and limitations of clinical fluoroscopy in arriving at a definite diagnosis are stressed.

This treatise is exceptionally well illustrated with a few simple line sketches and numerous photographs, which are unretouched, positive prints simulating the fluoroscopic image.

The bibliography is a complete and extensive one, rendering it valuable as a reference.

While this book is an excellent one, stressing the potentials and limitations of fluoroscopy, it will find its greatest appeal and use to roentgenologists and specialists in associated fields.

John M. Dennis, M.D.

Amputees and Prostheses: Report of a Conference on Prosthetics, Copenhagen, 23–28 August 1954. World Health Organization Technical Report Series No. 100. 52 pages; 16 × 24 cm. (paper-bound). World Health Organization, Geneva. Available in U. S. A. from Columbia University Press, International Documents Service, New York. 1955. Price, 60 cents.

This pamphlet contains a report of an international group of experts on the problem of the amputee and the methods "which have been or could be evolved for prevention of amputation and the reduction of disability resulting therefrom through

proper rehabilitation." It represents the combined thinking of 14 representatives from 10 different countries, who are all experts in their fields. All but two of the participants are physicians, mostly orthopedic surgeons interested in amputees. A well known prosthetist and social worker are also on the panel.

The report opens with a discussion of the incidence, cause and prevention of amputations, and the first annex contains a detailed report on the causes of amputations in various countries. This is followed by a discussion of the basic principles and practices for rehabilitation of the amputee, including surgical technics, pre and post amputation treatment (both psychological and physical), selection and prescription of the prosthesis, training in its use, follow-up adjustment and repair and vocational training and placement of the amputee. Other subjects reported and discussed more thoroughly in the annexes are: the essentials of a limb fitting service, the training of medical and prosthetic personnel, the design and type of artificial limbs, research and administrative problems.

The report is interesting and brings out most of the points considered important in treating an amputee, emphasizing the "social, economic, industrial and psychological problems affecting more people than those actually suffering the amputation."

FLORENCE I. MAHONEY, M.D.

Aspects of Allergy Research. Transactions of the Collegium Internationale Allergologicum: First Symposium in London, October 12–16, 1954. Edited by D. HARLEY, London, and P. KALLÓS, Helsingborg. 395 pages; 17.5 × 25 cm. (paper-bound). S. Karger, Basel. 1955. Price, $6.50.

These transactions of the First Symposium of The Collegium Internationale Allergologicum, entitled "Aspects of Allergy Research," are of some interest. The meeting was held at The Ciba Foundation in London and was apparently sponsored by that organization.

Not the least interesting feature of the meeting was its international flavor, the program including participants from Great Britain, the United States, Spain, Switzerland, Brazil and other countries. The range of subjects was wide, including a discussion of the dangers and disappointments of hayfever desensitization, histamine metabolism, serological problems in allergy, collagen disease, biochemistry of ACTH and cortisone, and numerous others.

For the reader interested in allergy and immunology the volume is informative. For others it may well be enlightening as evidence that allergy has made great strides and the modern developments warrant serious consideration of those attempting to treat this type of patient.

H. M. B.

Tumors of the Soft Tissues (Atlas of Tumor Pathology, Section II, Fascicle 5). By ARTHUR PURDY STOUT, M.D., Professor of Pathology, Columbia University, College of Physicians and Surgeons, New York City. 138 pages; 20 × 26 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the auspices of the Subcommittee on Oncology of the Committee on Pathology of the National Research Council, Washington 25, D. C. 1953. Price, $2.00.

This fascicle is formulated from a study of 8,686 tumors and tumor-like proliferations of soft tissues recorded in the Laboratory of Surgical Pathology of Columbia University over a period of 45½ years. The author briefly discusses the genesis of tumors of soft tissues and presents a broad classification of 7,337 benign mesenchymal tumors and 1,349 malignant tumors. Lipomatosis, fibromatosis and benign angiomatosis constitute the greater percentage of the benign mesenchymal tumors studied. Fibrosarcoma, liposarcoma, leiomyosarcoma and rhabdomyosarcoma make

up the greater number of malignant mesenchymal tumors in this series. A detailed description of each group and subgroup of tumors is presented and supported by numerous photographs and photomicrographs. This reviewer feels that the work serves as an excellent reference to a group of well classified mesenchymal tumors. The pathologist and general surgeon will find this volume a valuable addition to their libraries.

L. K.

The Clinical Care of the Diabetic. By JAMES J. SHORT, M.D., F.A.C.P., Associate Professor of Medicine, School of Medicine, College of Medical Evangelists, Senior Attending Physician, Los Angeles County General Hospital, Los Angeles, California. 84 pages; 13.5 × 20.5 cm. (leather-bound). San Lucas Press, Los Angeles. 1955. Price, $3.95.

The author summarizes in adequate detail his experiences in the treatment of patients with uncomplicated diabetes. One fourth of the volume consists of sample diets and menus. Discussion of etiology and pathogenesis omits, the author states, recent developments. Perfunctory treatment is given to acute and chronic complications, juvenile diabetes, surgery, and pregnancy (in which the use of diethylstilbestrol is stressed). A further discussion is given to diabetic acidosis in which the author believes that overindulgence in carbohydrates plays a part. Because of its emphasis on clinical essentials and its readability this monograph is of value to the clinician.

P. F.

The Care of Your Skin. By HERBERT LAWRENCE, M.D. 95 pages; 13 × 19.5 cm. Little, Brown and Company, Boston. 1955. Price, $2.50.

The major portion of this text is devoted to the etiology and the care of acne vulgaris, and to misconceptions concerning this condition. The author intelligently discusses the psychological aspects as well as other phases of acne which are usually neglected in standard textbooks. It is a text which has been intended primarily for the layman but physicians would also derive great benefit from reading this brief, well-written manuscript.

H. M. R.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

The Biliary Tract, With Special Reference to the Common Bile Duct. By JULIAN A. STERLING, A.B., M.D., M. Med. Sc., Sc.D., F.A.C.S., Staff Surgeon, Albert Einstein Medical Center and the Graduate Hospital, etc. 424 pages; 23.5 × 15.5 cm. 1955. The Williams & Wilkins Company, Baltimore. Price, $10.00.

Collected Papers on Aviation Medicine, Presented at Aeromedical Panel Meetings of the Advisory Group for Aeronautical Research and Development, Palais de Chaillot, Paris. 209 pages; 25 × 15 cm. 1955. Published for and on behalf of Advisory Group for Aeronautical Research and Development, North Atlantic Treaty Organization, by Butterworths Scientific Publications, London; available in U. S. A. from Interscience Publishers, Inc., New York. Price, $5.00.

Hand Surgery. Medical Department, United States Army. Surgery in World War II. Edited by STERLING BUNNELL, M.D. 447 pages; 25.5 × 17.5 cm. 1955. Office of the Surgeon General, Department of the Army, Washington, D. C. Price, $3.75 (buckram); for sale by the Superintendent of Documents, U. S. Government Printing Office, Washington, D. C.

Klinik und Therapie der Vergiftungen. By SVEN MOESCHLIN. 521 pages; 24.5 × 17.5 cm. 1956. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. Price, Ganzleinen DM 59.–

Koronarthrombose Cor Pulmonale. Verhandlungen der Deutschen Gesellschaft für Kreislaufforschung. 21. Tagung Bad Nauheim Vom. 15. Bis 17. April 1955. Edited by PROF. DR. RUDOLF THAUER. 484 pages; 22.5 × 15.5 cm. (paperbound). 1955. Verlag Dr. Dietrich Steinkopff, Darmstadt. Price, Brosch DM 56.–

Life Stress and Essential Hypertension: A Study of Circulatory Adjustments in Man. By STEWART WOLF, M.D., Professor and Head, Department of Medicine, University of Oklahoma School of Medicine, etc.; PHILIPPE V. CARDON, JR., M.D., Senior Assistant Surgeon (R), USPHS, National Institute of Mental Health, National Institutes of Health, Bethesda, Md., etc.; EDWARD M. SHEPARD, M.D., Instructor in Medicine, Cornell University Medical College, etc.; and HAROLD G. WOLFF, M.D., Professor of Medicine (Neurology), Cornell University Medical College, etc. 253 pages; 23.5 × 15.5 cm. 1955. The Williams & Wilkins Company, Baltimore. Price, $7.50.

A Stereoscopic Atlas of Human Anatomy. Section III: The Upper Extremity, With 196 Stereoscopic Transparencies in Full Color, View-Master 3-Dimension Viewer, View-Master Light Attachment for Model E Viewer, Two No. 1550 Olin Leakproof Batteries. By DAVID L. BASSETT, M.D. 1955. Sawyer's Inc., Portland, Oregon. Price, $22.50.

Topley and Wilson's Principles of Bacteriology and Immunity. 4th Ed., in two volumes. By G. S. WILSON, M.D., F.R.C.P., D.P.H., Director of the Public Health Laboratory Service, England and Wales; and A. A. MILES, C.B.E., M.A., M.D., F.R.C.P., Professor of Experimental Pathology, University of London, etc. 2,379 pages; 25 × 17 cm. 1955. The Williams & Wilkins Company, Baltimore. Price, $24.50.

COLLEGE NEWS NOTES

New Life Members

The College is gratified to have as new Life Members the following Fellows:

Dr. W. Price Killingsworth, Port Arthur, Tex.
Dr. John C. Wilt, Winnipeg, Man., Canada
Dr. DeForest R. Hastings, Minneapolis, Minn.
Dr. Louis D. Fey, Seattle, Wash.
Dr. Wade H. Boswell, Knoxville, Tenn.
Dr. Paul F. Miner, Boise, Idaho

The names of all Life Members are inscribed in an especially prepared volume that may be examined in the College Booth during the Annual Session.

Gifts to College Library of Publications by Members

The College expresses its appreciation to the following members who have presented autographed copies of their books to the College Library of Publications by Members:

Clifford J. Barborka, M.D., F.A.C.P., Chicago, Ill.—*Peptic Ulcer: Diagnosis and Treatment*, co-authored with E. Clinton Texter, Jr., M.D.

Bernard S. Lipman, M.D., F.A.C.P., Atlanta, Ga.—*Clinical Unipolar Electrocardiography*, co-authored with Edward Massie, M.D., F.A.C.P., St. Louis, Mo. (2nd Edition, Japanese Translation.)

Proposals of Candidates

Regulations prescribe that proposals of candidates must reach the Executive Offices of the College 60 days in advance of action. The Committee on Credentials met on March 17–18, 1956, and will meet again at Los Angeles, April 13–14, 1956. Obviously, it is now too late to receive proposals of candidates for action at Los Angeles.

The Committee on Credentials will meet again on Nov. 10–11, 1956, at which time all proposals filed between Feb. 13 and Sept. 10, 1956, will be acted upon.

President Appoints Dr. John N. Compton as Governor for Arkansas

In accordance with the By Laws of the College, President George F. Strong has appointed Dr. John N. Compton, F.A.C.P., Little Rock, Governor for Arkansas to succeed the late Dr. Arless Arland Blair, and to serve until the next regular election, which will take place at the Annual Business Meeting at Los Angeles, April 19, 1956.

Philadelphia Medico-Legal Institute

The Philadelphia Medico-Legal Institute is being incorporated as a non-profit corporation. Its chief purpose is to encourage research, professional training and teaching in the field of forensic medicine, and promote better understanding between the professions of law and medicine generally, and to explore means for effecting a

closer and more beneficial working relation between lawyers and physicians. The Philadelphia Bar Association and the Philadelphia County Medical Society are the coöperating bodies. Dr. Samuel B. Hadden, F.A.C.P., is Vice President. Among the medical representatives are: Dr. David A. Cooper, F.A.C.P., Dr. Richard A. Kern, F.A.C.P., Dr. Baldwin L. Keyes, F.A.C.P., Dr. Norbert J. Roberts (Associate), and Dr. Truman G. Schnabel, F.A.C.P.

The total elected membership will be limited to 500 persons, and neither profession, law nor medicine, shall represent more than 60% of the total elected membership. Candidates must be proposed in writing by a member, seconded by another member, and endorsed by the Committee on Membership. Annual dues will be $5.00.

Coming A.C.P. Regional Meetings

Date	*Territory*	*Governor*	*Official Guest*
Mar. 24	S. ILLINOIS, Springfield	C. H. Drenckhahn, M.D.	.....
Sept. 8	NORTH DAKOTA, Minot	.....	.....
Oct. 19	WESTERN NEW YORK, Albany	John H. Talbott, M.D.	.....
Oct. 27	MIDWEST, Minneapolis (Ill., Ind., Iowa, Minn., Wis.)	Wesley W. Spink, M.D.	Walter L. Palmer, M.D., President E. R. Loveland, Executive Secretary
Nov. 7	NEW JERSEY, Newark	E. C. Klein, Jr., M.D.	.....
Dec. 6	NORTH CAROLINA, Chapel Hill	Elbert L. Persons, M.D.	.....

Others scheduled but dates not yet determined include KENTUCKY-TENNESSEE at Nashville; MICHIGAN at Ann Arbor; NEW ENGLAND at Burlington, Vt.

Examinations by Certifying Boards

The American Board of Internal Medicine, William A. Werrell, M.D., Executive Secretary-Treasurer, 1 W. Main St., Madison 3, Wis. Written Examination, Oct. 15, 1956. Final date for filing application is May 1. Oral Examinations: Los Angeles, April 12–14; Chicago, June 7–9. Final date for filing these applications was Jan. 3. New York City, Sept. 21–25. Final date for filing application is April 1.

The American Board of Dermatology and Syphilology, B. M. Kesten, M.D., 1 Haven Ave., New York 32, N. Y. Written Examination: Various centers, July 26. Oral Examination: St. Louis, Oct. 12–15. Final date for filing applications is April 1.

The American Board of Physical Medicine and Rehabilitation, Earl C. Elkins, M.D., 200 First St., S. W., Rochester, Minn. Parts I and II: Chicago, June 16–17.

The American Board of Psychiatry and Neurology, David A. Boyd, M.D., 102–110 Second Ave., S.W., Rochester, Minn. Philadelphia, April 16–18.

The American Board of Radiology, B. R. Kirklin, M.D., Kahler Hotel Bldg., Rochester, Minn. Chicago, June 5–9. Final date for filing application was Jan. 1. Los Angeles, Sept. 30–Oct. 4. Final date for filing application is June 1.

Additional Contributions to the Willard O. Thompson Memorial Scholarship Fund

Additional contributions amounting to $110.00 have been made by friends or patients to the Willard O. Thompson Memorial Traveling Scholarship Fund of the American College of Physicians. The Fund has considerably passed the original objective. Already, a traveling Fellow in Endocrinology has been appointed for 1956.

Bibliography of Medical Reviews

The Armed Forces Medical Library announces the publication in May of a *Bibliography of Medical Reviews*. The bibliography, arranged by subject, will contain approximately 800 references to review articles in clinical and experimental medicine and allied fields which have appeared in the calendar year 1955.

Copies of the *Bibliography of Medical Reviews* will be available upon request to the Director, Armed Forces Medical Library, 7th St. & Independence Ave., S.W., Washington 25, D. C., in the order of receipt.

Residencies in Psychiatry

The Veterans Administration Hospital, Lyons, N. J., has available residencies in Psychiatry for a one to three year period which are fully accredited by the American Board of Psychiatry and Neurology. The training program consists of lectures, conferences and seminars under the direction of the Department of Psychiatry, New York Medical College, Flower and Fifth Avenue Hospitals, and offers intensive training, both intramurally and through rotation in special hospitals and clinics in the adjacent area. There is, in addition, a series of extensive guest lecturers as well as an Annual Institute at this hospital. Training may commence at any time.

Dr. Josephine C. Lawney, F.A.C.P., a missionary doctor in Shanghai, China, for 30 years, was honored recently by her alma mater, Woman's Medical College of Pennsylvania, Philadelphia. Throughout the 105 years of its history this College has been notable for the number of graduates who have gone into missionary service. Dr. Lawney received two citations, one from the President and one from the Dean; also the honorary degree of Sc.D. (Medicine) was conferred upon her. She began her service with the Woman's American Baptist Foreign Mission Society in 1919 as one of the outstanding doctors in the interdenominational Woman's Christian Medical College and the Margaret Williamson Hospital, Shanghai. Dr. Lawney now resides at Roslyn Heights, L. I., N. Y.

Four Fellows of the College have recently been appointed by the Veterans Administration to an advisory committee to counsel the Chief Medical Director concerning research programs within the Administration. They are: Dr. Joseph M. Hayman, Jr., Boston, who is Chairman; Dr. J. Burns Amberson, New York City; Dr. W. Reece Berryhill, Chapel Hill, N. C.; and Dr. Harold G. Wolff, New York City.

Dr. Jean-Baptiste Jobin, F.A.C.P., F.R.C.P.(C), dean of the Faculty of Medicine of Laval University (Quebec, Canada) is the new medical director of the Hôtel-Dieu de Québec (Quebec, Canada).

Dr. Frank W. Reynolds, F.A.C.P., Albany, N. Y., recently served as Consultant to the European Office of the World Health Organization, reviewing the progress of WHO-assisted projects in Morocco. Dr. Reynolds is presently Director of the Bureau of Chronic Diseases and Geriatrics of the New York State Department of Health.

Dr. Paul A. Burgeson, F.A.C.P., Warsaw, N. Y., has been appointed Chief of Staff at the Wyoming County Community Hospital, having been Chief of Medical Services since 1947.

Dr. Herbert R. Edwards, F.A.C.P., New Haven, Conn., has been appointed Associate Professor of Medicine and Public Health at Yale University. His responsibilities will include teaching, research, and consultation with special emphasis on tuberculosis control at the Yale-New Haven Medical Center and in the New Haven area.

Dr. Leon H. Warren, F.A.C.P., formerly of Philadelphia, has recently been appointed Associate in the Clinical Investigation Department of Parke, Davis & Company, it was announced by Dr. E. C. Vonder Heide, Department Director. Dr. Warren is a specialist in skin diseases, and has been with the National Research Council for the past four years as Staff Officer in charge of activities of the Committee on Medicine and Surgery.

Dr. James L. Wade, F.A.C.P., Parkersburg, W. Va., has been named Parliamentarian of the West Virginia State Medical Association for the year 1956.

Dr. John R. Laadt (Associate) has recently been appointed to the staff of Passavant Memorial Hospital, Chicago.

Drs. Louis P. Hastings, F.A.C.P., of Hartford, Conn., and John P. Hubbard, F.A.C.P., of Philadelphia, spoke before the Connecticut State Medical Society on "The State License" and the "National Board of Medical Examiners," respectively. The session was held at the Yale University School of Medicine, Jan. 5, 1956.

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., former President of the American College of Physicians, spent three weeks in December in Rio de Janeiro where he delivered a series of six lectures and participated in a number of round table exercises and ward rounds.

Dr. Harold Jeghers, F.A.C.P., Professor of Medicine and Director of the Department, Georgetown University School of Medicine, Washington, D. C., on December 1, 1955, addressed the Mercy Hospital staff, Baltimore, Md., on the subject, "Hemoptysis," and on December 8, 1955 addressed the Carney Hospital staff, Boston, Mass., on the subject, "The Philosophy of Graduate Medical Education."

Dr. Jackson A. Smith (Associate), formerly of Houston, Tex., has joined the staff of the University of Nebraska College of Medicine as Professor of Neurology

and Psychiatry and Director of Research of the Nebraska Psychiatric Institute. Dr. Smith, as Director, will develop a psychiatric research program on a state-wide basis; research now under way includes the study of geriatric problems and problems of emotionally disturbed children.

Dr. J. Burns Amberson, F.A.C.P., New York City, has been appointed Director of the New York Tuberculosis and Health Association. Dr. Amberson recently retired from his positions at the Presbyterian Hospital and Columbia University College of Physicians and Surgeons, becoming Consultant at the Hospital and Professor Emeritus at the College.

Dr. Samuel J. Prigal, F.A.C.P., New York City, and Dr. Joseph H. Fries, F.A.C.P., Brooklyn, were elected President-Elect and Treasurer, respectively, of The New York Allergy Society.

Drs. Donald J. Wilson, F.A.C.P., and Edmond M. Walsh, F.A.C.P., both of Omaha, have been elected to the Executive Committee of the Omaha Mid-West Clinical Society. Drs. Harold N. Neu, F.A.C.P., and Henry J. Lehnhoff, Jr., F.A.C.P., also of Omaha, were elected Co-Chairmen of the Section on Medicine.

Drs. James M. Moss, F.A.C.P., Alexandria, Va., and Louis K. Alpert, F.A.C.P., Washington, D. C., have recently been elected Vice President and Secretary-Treasurer, respectively, of the Clinical Society of the Diabetes Association of the District of Columbia.

Dr. June C. Shafer, F.A.C.P., Arlington, Va., was elected to the Board of Directors of the American Academy of Dermatology and Syphilology at the annual meeting held in Chicago, Dec. 5–8, 1955.

Dr. Cyrus C. Sturgis, F.A.C.P., Ann Arbor, Mich., has served as Visiting Professor of Internal Medicine at Baylor University College of Medicine, Jan. 22–27. Dr. Sturgis is the first to fill the Visiting Professorship of Internal Medicine at the College, established in the memory of Mr. and Mrs. J. N. Taub.

The University of California Medical Center, San Francisco, offered two short postgraduate courses between March 19–23, 1956, entitled, respectively, "Clinical Electrocardiography" and "Bedside Cardiology." The tuition fee for the first course was $50.00, and for the second course $100.00. Many Fellows of the College appeared on the faculties.

Dr. Samuel A. Levine, F.A.C.P., Boston, Mass., gave a course in Practical Bedside Cardiology at the Texas Medical Center, Houston, March 14–17. Also on the program were: Drs. Sidney Schnur, F.A.C.P., Stanley W. Olson, F.A.C.P., Hatch W. Cummings, Jr., F.A.C.P., Hugh Bennett, F.A.C.P., and James A. Greene, F.A.C.P., all of Houston.

A medical symposium of national importance was held in Cincinnati, Ohio, on Jan. 13. The symposium covered "Constructive Medicine in Aging," along with a discussion of "Problems of the Mind in Later Life." On the program were the

following members of the College with their respective papers: Dr. Franklin G. Ebaugh, F.A.C.P., Denver, "Age Introduces Stress into the Family"; Dr. Edward Weiss, F.A.C.P., Philadelphia, "Consequences of Anxiety"; Capt. George N. Raines, (MC), USN, F.A.C.P., "Adolescence: Pattern for the Future"; and Dr. Ewald W. Busse, F.A.C.P., Durham, N. C., "Care of the Non-Hospitalized Mentally Ill Aged Patient." Dr. Edward J. Stieglitz, F.A.C.P., Washington, D. C., moderated a panel discussion and summed up the symposium. This Second Annual Gerontological symposium was sponsored by the Wm. S. Merrell Company of Cincinnati.

Dr. Walter Bauer, F.A.C.P., and Dr. Samuel A. Levine, F.A.C.P., both of Boston, Mass., and Dr. H. Marvin Pollard, F.A.C.P., Ann Arbor, A.C.P. Governor for Michigan, spoke at the Spring Clinical Conference of the Dallas Southern Clinical Society held at Dallas, Texas, March 12–14, on their respective specialties of Internal Medicine, Cardiology and Gastroenterology.

Dr. Walter C. Alvarez, F.A.C.P., Chicago, Ill., discussed "Role of the General Practitioner" at the dedication ceremonies of the recently completed Olmstead Community Hospital, Rochester, Minn.

COMING EVENTS, 1956

April 16–20 American College of Physicians, Los Angeles, Calif.; Mr. E. R. Loveland, 4200 Pine St., Philadelphia 4, Pa.

April 15–20 American College of Allergists, New York, N. Y.; Dr. F. W. Wittich, Secretary, 401 Marquette Bank Bldg., Minneapolis 2, Minn.

April 23–28 American Academy of Neurology, St. Louis, Mo.; Dr. T. W. Farmer, Secretary, University of North Carolina, Chapel Hill, N. C.

April 25–28 American Association of Pathologists and Bacteriologists, Cincinnati, Ohio; Dr. Edward A. Gall, Secretary, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 27–28 American Gastro-enterological Association, Atlantic City, N. J.; Dr. H. Marvin Pollard, Secretary, University Hospital, Ann Arbor, Mich.

April 30–May 4 American Psychiatric Association, Chicago, Ill.; Dr. William Malamud, Secretary, 80 E. Concord St., Boston 18, Mass.

May 3–4 American Geriatrics Society, Chicago, Ill.; Dr. Malford W. Thewlis, Secretary, 25 Mechanic St., Wakefield, R. I.

May 6–11 American Pediatric Society, Buck Hill Falls, Pa.; Dr. A. C. McGuinness, 1427 Eye St., N.W., Washington 5, D. C.

May 28–June 1 First International Symposium on Venereal Diseases and the Treponematoses, under joint sponsorship of the U. S. Public Health Service and the World Health Organization, Statler Hotel, Washington, D. C.; Dr. C. A. Smith, Medical Director, Division of Special Health Services, Department of Health, Education and Welfare, Washington 25, D. C.

June 7–10 American College of Chest Physicians, Chicago, Ill.; Mr. Murray Kornfeld, Secretary, 112 E. Chestnut St., Chicago 11, Ill.

June 9–10 American Diabetes Association, Chicago, Ill.; Dr. F. B. Peck, Sr., 1 E. 45th St., New York 17, N. Y.

June 9 American Academy of Tuberculosis Physicians, Chicago, Ill.; Dr. Oscar S. Levin, Secretary, P. O. Box 7011, Denver 6, Colo.

June 10–14 Canadian Medical Association, Quebec, P.Q., Canada; Dr. Arthur D. Kelly, Secretary, 150 St. George St., Toronto 5, Ont., Can.

June 11–15 American Medical Association, Chicago, Ill.; (Clinical Session, Nov. 27–30, Seattle, Wash.); Dr. George F. Lull, Secretary, 535 N. Dearborn St., Chicago 10, Ill.

June 18–21 American Dermatological Association, Santa Barbara, Calif.; Dr. J. Lamar Callaway, Secretary, Duke Hospital, Durham, N. C.

June 18–20 American Neurological Association, Atlantic City, N. J.; Dr. Charles Rupp, Secretary, 133 S. 36th St., Philadelphia 4, Pa.

Sept. 3–8 International Congress of Haematology, Boston, Mass.; address the Congress, c/o Harrison Ave. & Bennet St., Boston 11, Mass.

Sept. 10–14 American Congress of Physical Medicine and Rehabilitation, Atlantic City, N. J.; Dr. Frances Baker, Secretary, 1 Tilton Ave., San Mateo, Calif.

Oct. 8–11 American Academy of Pediatrics, New York, N. Y.; Dr. E. H. Christopherson, Secretary, 610 Church St., Evanston, Ill.

Oct. 9–15 World Medical Association, Havana, Cuba; Dr. Louis H. Bauer, Secretary-General, 345 E. 46th St., New York 17, N. Y.

Oct. 14 American College of Gastro-enterology, New York, N. Y.; Mr. Daniel Weiss, Secretary, 33 W. 60th St., New York 23, N. Y.

Nov. 4–10 Inter-American Congress of Cardiology, Havana, Cuba; Dr. Ramon Aixala, Apartado 2108, Havana, Cuba.

Foreign

May 1–5 National Congress of Pediatrics, Cuidad Universitaria, Mexico, D. F., Mexico; Dr. Ignacio Avila Cianeros, Co-ordinator, Calzada de Madereros No. 240, Mexico 18, D. F., Mexico.

July 18–21 International Congress of Gastro-enterology, London, England; Mr. Hermon Taylor, Honorable Secretary, London Hospital, White Chapel, London E. 1, England.

July 22–28 International Congress of Radiology, Mexico, D.F., Mexico; Dr. Jose Noriega, Secretary-General, Tepic 126 (2e piso), Mexico 7, D. F., Mexico.

Aug. 19–23 International Congress of Diseases of the Chest, Cologne, Germany; Mr. Murray Kornfeld, Executive Director, 112 E. Chestnut St., Chicago 11, Ill.

Aug. 20–24 International Congress of Physical Medicine, Copenhagen, Denmark; Dr. B. Strandberg, Honorable Secretary, Kobenhavns amts sygehus Gentofte, Dept. of Rheumatology and Physical Medicine, Hellerup, Denmark.

Sept. 10–14 International Congress of Dietetics, Congress Palace, Esposizione Universale Roma, Rome, Italy; Prof. E. Serianni, Secretary-General, Associazione Dietetica, Italiana, via dei Penitenzieri, N. 13, Rome, Italy.

Sept. 10–14 Second Congress, European Society of Cardiology, Stockholm, Sweden; Prof. K. E. Grewin, Sodersjukhuset, Stockholm, Sweden.

Sept. 10–15 International Congress Against Alcoholism, Istambul, Turkey; International contre l'Alcoolisme, Case Gare 49, Lausanne, Switzerland.

Sept. 12–15 European Congress of Allergology, Florence, Italy; Prof. Umberto Serafini, Secretary-General, Instituto de Patollogia Medica, Viale Morgagni, Florence, Italy.

Sept. 19–23 International Congress of Internal Medicine, Madrid, Spain; Dr. J. C. De Oya, Secretary, Hostaleza No. 90, Madrid, Spain.

Sept. 25–29 Association of Industrial Medical Officers, 21st anniversary meeting, London, England; Dr. P. A. B. Raffle, London Transport Executive, Griffith House, 280 Marylebone Rd., London, N.W. 1, England.

Oct. 4–6 Association of Clinical Pathologists, London, England; Dr. W. H. McMenemey, Maida Vale Hospital for Nervous Diseases, London, W. 9, England.

The First International Congress of Human Genetics will be held in Copenhagen, Denmark, August 1–6, 1956. This congress is planned to cover all genetic aspects of normal and pathological characters in man. Any person interested in the subject of human genetics and especially of medical genetics is invited to take part in the congress.

Provisional program and further information are sent on request. The Secretariate of the First International Congress of Human Genetics, The University Institute for Human Genetics, 14, Tagensvej, Copenhagen, N., Denmark.

OBITUARIES

RECENT DEATHS OF A.C.P. MEMBERS

The College records with sorrow the deaths of the following members. Their obituaries will appear later in these columns.

Dr. William R. C. Neumarker, (Associate), Columbus, Nebr. Date Not Recorded
Dr. James A. Lyon, F.A.C.P., Washington, D. C., Aug. 3, 1955
Dr. Fred B. Wilson, F.A.C.P., Beaver, Pa., Aug. 18, 1955
Dr. Virgil G. Presson, F.A.C.P., Tucson, Ariz., Oct. 2, 1955
Dr. Thomas T. Mackie, F.A.C.P., West Port, Conn., Oct. 5, 1955
Dr. Walter D. Ford, F.A.C.P., Dearborn, Mich., Oct. 12, 1955
Dr. Siegfried Block, F.A.C.P., New York, N. Y., Oct. 18, 1955
Dr. Walter C. Smallwood, F.A.C.P., Longbeach, Calif., Oct. 25, 1955
Dr. William Maris, (Associate), Sioux Center, Iowa, Oct. 29, 1955
Dr. Frederick R. Taylor, F.A.C.P., High Point, N. C., Nov. 1, 1955
Dr. Leo E. Westcott, F.A.C.P., Kalamazoo, Mich., Nov. 6, 1955
Dr. Philip W. Flagge, F.A.C.P., Laramie, Wyo., Nov. 15, 1955
Dr. Oscar B. Ragins, F.A.C.P., Chicago, Ill., Nov. 18, 1955
Dr. Alfred L. Kruger, Sr., F.A.C.P., Norfolk, Va., Dec. 25, 1955
Dr. Haydn H. Cutler, F.A.C.P., Monroe, La., Dec. 30, 1955
Dr. Samuel E. Thompson, F.A.C.P., Kerrville, Tex., Jan. 12, 1956

DR. PETER T. BOHAN

Peter Thomas Bohan, M.D., F.A.C.P., of Kansas City, Mo., died on Oct. 2, 1955, after an acute myocardial infarction.

Dr. Bohan was born in Henderson County, Ill., on Jan. 16, 1874. He was graduated from Rush Medical College in 1900, was a member of the house staff of the Alexian Brothers Hospital in Chicago from 1900–02, and then studied for several years in Vienna. In 1909 he began 45 years of service at the University of Kansas School of Medicine, where he held the rank of Professor of Clinical Medicine from 1916 until he became Emeritus Professor in 1954. He was a dramatic, vigorous, outstanding teacher of medicine. He loved to teach, and his students loved him. There was never a dull moment in his clinics. Former students and friends expressed their appreciation to him a few years ago by establishing an endowed annual lecture in his honor at the University of Kansas.

Dr. Bohan's warm personality and his keen judgment won for him unusual admiration by his patients. His medical associates found his debates on medical subjects stimulating, punctuated with definite ideas, well expressed. They honored him by electing him President of the Kansas City Academy of Medicine, of the Jackson County Medical Society, and of the Kansas City Southwest Clinical Society. Dr. Bohan became a Fellow of the American College of Physicians in 1924. His hospital appointments were to the St. Luke's, Research, Kansas City General, and St. Margaret's Hospitals; at the latter, he was Physician-in-Chief from 1910–18.

Dr. Bohan is survived by his wife, Ruth, of 420 E. Armour Blvd., E., herself a talented artist, a devoted companion, and a constant helper.

CARL V. MOORE, M.D., F.A.C.P.,
Governor for Missouri

DR. JULIUS H. HESS

Dr. Julius Hays Hess, F.A.C.P., of Chicago, died of coronary artery disease while visiting in Los Angeles on Nov. 2, 1955, age 79. Dr. Hess was born in Ottawa, Ill., Jan. 26, 1876. He received his M.D. degree at Northwestern University Medical School in Chicago in 1899. He served an internship at Alexian Brothers Hospital in Chicago and continued postgraduate work at the Johns Hopkins Hospital in Baltimore and at European clinics.

Very early in his career, Dr. Hess decided to specialize in pediatrics and joined the faculty of the University of Illinois College of Medicine in 1913. In 1916 he became Professor and Chairman of the Department of Pediatrics at Illinois and served in that capacity until 1944 when he became Emeritus Professor.

Dr. Hess was a Diplomate of the American Board of Pediatrics and became a Fellow of the American College of Physicians in 1926. All his professional life he was interested in the problems of the prematurely born infant. He received many honors, among them the Borden Award by the American Academy of Pediatrics.

In 1935–36 Dr. Hess was President of the Chicago Medical Society and later Vice President of the Institute of Medicine of Chicago. He served his local, state and national medical organizations in many capacities. Up to the time of his death, he was still fairly active in pediatric practice.

He served with distinction on the staffs of Michael Reese Hospital, Cook County Hospital and other institutions. He contributed freely to the pediatric literature, i.e., systems in pediatrics, papers, monographs and books.

During World War I Dr. Hess was a Major in the Medical Corps of the United States Army and was Commanding Officer of General Hospital No. 25.

A man who was so active as Dr. Hess on so many fronts will be greatly missed, not only in Chicago but in the entire country. His pattern of life is a great example to all of us.

Dr. Hess is survived by his widow, Clara, who lives at the Hotel Windermere East, 1642 E. 56th St., Chicago 37, and two daughters, Mrs. Jean Spencer and Mrs. Carol Saphir.

HOWARD WAKEFIELD, M.D., F.A.C.P.,
Governor for Northern Illinois

DR. CHARLES N. KAVANAUGH

Dr. Charles Nicholas Kavanaugh, F.A.C.P., died at his home in Lexington, Ky., on Oct. 29, 1955, following coronary thrombosis. He had been in good health and actively engaged in his work up to less than an hour before his death.

Dr. Kavanaugh was born in Lawrenceburg, Ky., Feb. 13, 1892. He was graduated from the University of Louisville School of Medicine in 1915 and served his internship at Louisville General Hospital. Following this in 1917, he entered the United States Armed Forces with the rank of Lieutenant and served during World War I, largely in France, being separated from the service with the rank of Major. After the war he resumed his postgraduate training as medical resident at Boston City Hospital and at Massachusetts General Hospital. He continued postgraduate studies, largely in his chosen specialty of cardiology, throughout his life. These studies included work under Dr. Paul Dudley White, M.A.C.P., in Boston, Dr. Parkinson in London and, during his last summer, under Dr. Chiari in Vienna. He was a Diplomate of the American Board of Internal Medicine and became a Fellow of the American College of Physicians in 1927.

Dr. Kavanaugh was associated throughout his years of medical practice with the Lexington Clinic as Internist and Cardiologist. His standing in the profession was attested by his appointments, which included Associate Chief of Medical Service and Consulting Cardiologist at Good Samaritan Hospital, Consultant in Cardiology

to St. Joseph Infirmary, Central Baptist and U. S. Public Health Service Hospitals, and Consulting Physician to Eastern State Hospital, all of Lexington; he was also a member of the Medical Advisory Board of the Frontier Nursing Service, Wendover, Ky. His sound judgment and broad knowledge of medicine made him a consultant highly valued by physicians, not only in Lexington but throughout central and eastern Kentucky.

Dr. Kavanaugh attained distinction not only in medicine but also in his avocations. He was best known as an amateur photographer and his work had received recognition in national exhibitions. He was particularly noted for his keen artistry in composition. His pictures grace the walls of many of his friends' homes and offices. An earlier interest was in prehistoric man in Kentucky, and working with the Department of Archeology at the University of Kentucky, he assisted in the excavation and study of prehistoric sites. He was a quiet man with a keen and kindly humor. His wide associations brought him a host of friends, both within and without the medical profession, to all of whom he was affectionately known as "Mike."

Dr. Kavanaugh is survived by his widow, Mrs. Elizabeth Kavanaugh, 227 S. Ashland Ave., Louisville, and by three sons.

CARL H. FORTUNE, M.D., F.A.C.P.

DR. HENRY A. LUCE

Henry A. Luce, M.D., F.A.C.P., was born in the little town of Linden, Mich., on Oct. 16, 1875, and died in Detroit on Oct. 28, 1955.

Dr. Luce started the study of medicine at the Detroit College of Medicine and Surgery, now Wayne University College of Medicine, in 1901 and graduated with his M.D. degree in 1905. He spent his entire medical life in Detroit; starting as a general practitioner, he gravitated naturally to internal medicine and then became a pioneer specialist in neuropsychiatry, in which he became an outstanding leader.

Dr. Luce was on the staff of Wayne County General, Receiving, Evangelical Deaconess, and Harper Hospitals. He was a Diplomate of the American Board of Psychiatry and Neurology and became a Fellow of the American College of Physicians in 1926. He was a member of the Wayne County Medical Society and its President in 1925–26. He was also a delegate from Wayne County to the Michigan State Medical Society for many years. He was elected President of the Michigan State Medical Society for the period 1938–39. The doctor served as delegate from Michigan to the A.M.A. for eighteen years, during which time he was instrumental in helping to solve numerous medical problems.

Among his many accomplishments was his appointment by President Franklin D. Roosevelt as a medical member of the first National Conference on Economic Security in 1934. In the same year, this writer remembers how Dr. Luce suddenly left his practice and went with a group to England, France, and Italy to study medical services in these countries. The report of this committee was of great interest and help to the medical profession in the United States.

In 1943, he served as President of the Michigan Society of Psychiatry and Neurology. He was a past President of the Detroit Academy of Medicine and a member of the Detroit Medical Club and various civic organizations.

What about the man himself? The writer knew Dr. Luce nearly all his medical life. First contacts went back to the days of the Pennsylvania Sanatorium and continued to the end of his days. A relative needed his special service and we will always remember his kind and understanding care of the case. The doctor was able in a short time to gain the confidence of the patient. As a result of his skill, the patient has been well and happy for these many years.

Dr. Luce was an intensely human being, interested in his patients' welfare, and he took the time to study each one of them. They all loved him; many told me so.

He was a fighter, also, when it became necessary to defend his position and what he thought was right. Even in argument, however, he was self-controlled. The expression "steel hand in a velvet glove" was used to express his argumental procedure. Besides being a distinguished medical man, the doctor was a medical statesman as shown by his many contributions to medicine, medical economics, and to his specialty.

In the death of Dr. Luce, medicine lost a gentleman, a scholar, and a distinguished leader, for he was a true follower of the Great Physician. He spent his life in helping others, and his many friends and patients will miss him sadly.

"A man so various that he seemed to be
Not one, but all mankind's epitome."—Dryden

William J. Stapleton, Jr., M.D., F.A.C.P.

DR. JAMES W. VERNON

Dr. James William Vernon, F.A.C.P., of Morganton, N. C., died of a cerebrovascular accident on July 16, 1955, shortly before his 69th birthday and after a life in which he was a leading citizen as well as an outstanding medical specialist. He was Mayor of Morganton from 1933–37 and President of the Medical Society of the State of North Carolina in 1943–44.

Dr. Vernon was born in Person County, N. C., July 21, 1886, and received his B.S. degree from Wake Forest College in 1907 and his M.D. from Jefferson Medical College of Philadelphia in 1909. He was a pioneer in the field of psychiatry in North Carolina and, after service in France during World War I, became Superintendent and Medical Director of Broadoaks Sanatorium in 1921. As the North Carolina psychiatric hospital service developed, he became a Consulting Psychiatrist in the State Hospital at Morganton in 1936 and a member of the Advisory Committee of the North Carolina Hospitals Board of Control in 1945. He became a Fellow of the American College of Physicians in 1933 (Life Member, 1944) and was accepted as a Diplomate of the American Board of Psychiatry and Neurology when it was instituted.

He had served as President of the Burke County Medical Society and as a surgeon to the Southern Railway and was examining physician for the Burke County Selective Service Board during World War II. He was a member of the Tri-State Medical Society, Southern and American Medical Associations, Southern Psychiatric Association and the National Committee for Mental Hygiene, as well as the American Ornithologists Union, American Association for the Advancement of Science, and the North Carolina Academy of Science.

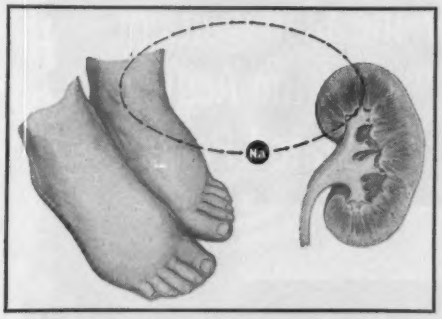
Dr. Vernon is survived by his widow, Mrs. Sarah T. Vernon, 209 Valdese Ave., Morganton. Many practicing physicians are grateful for his understanding and support in the management of psychiatric problems during the years when these problems were regarded as different from those of a physician.

Elbert L. Persons, M.D., F.A.C.P.,
Governor for North Carolina

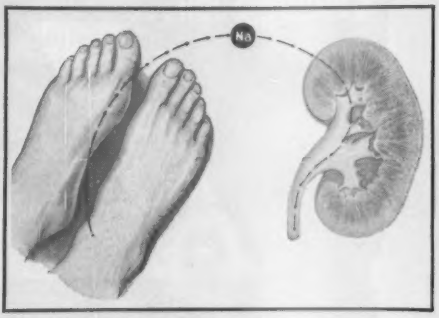
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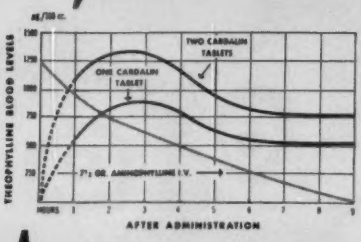
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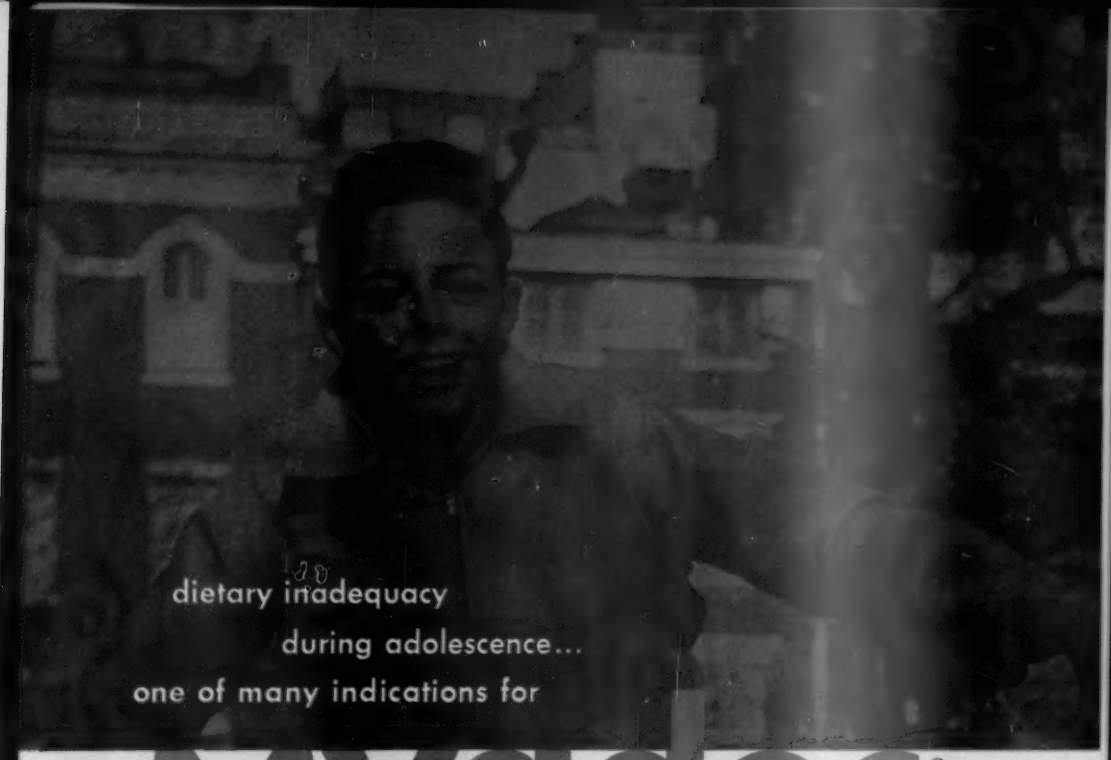
SCHEDULE OF POSTGRADUATE COURSES, SPRING, 1956

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	March				April				May					June		
	5–9	12–16	19–24	26–30	2–6	9–13	16–20	23–27	Apr. 30–4	7–11	14–18	21–25	28–June 1	4–8	11–15	18–23
Course No. 1, SELECTED SUBJECTS IN INTERNAL MEDICINE: Columbia University College of Physicians and Surgeons and Presbyterian Hospital, New York, N. Y.; Franklin M. Hanger, M.D., F.A.C.P., and Robert F. Loeb, M.D., F.A.C.P., Co-directors.		X			Easter Week—Easter, April 1		Annual Session, The American College of Physicians, Los Angeles								Annual Meeting, American Medical Association, Chicago	
Course No. 2, THE HEART: RECENT ADVANCES IN DIAGNOSIS AND TREATMENT: University of Kansas Medical Center, Kansas City, Kans.; E. Grey Dimond, M.D., F.A.C.P., Director.			19–23													
Course No. 3, ISOTOPES IN CLINICAL MEDICINE: Ohio State University College of Medicine, Columbus, Ohio; Charles A. Doan, M.D., F.A.C.P., William G. Myers, M.D., F.A.C.P., and Bruce K. Wiseman, M.D., F.A.C.P., Co-directors.			A X	B X												
Course No. 4, RADIOLOGY IN INTERNAL MEDICINE: University of Oregon Medical School, Portland, Ore.; Charles Dotter, M.D., and Howard P. Lewis, M.D., F.A.C.P., Co-directors.						X										
Course No. 5, SOME RECENT DEVELOPMENTS IN PRINCIPLES AND PRACTICE OF MODERN MEDICINE: Pennsylvania Hospital, Philadelphia, Pa.; Garfield G. Duncan, M.D., F.A.C.P., Director.											X					
Course No. 6, ADVANCES IN ELECTROCARDIOGRAPHY: New York University—Bellevue Medical Center, New York, N. Y.; Charles E. Kossmann, M.D., F.A.C.P., Director.														X		
Course No. 7, ENDOCRINOLOGY: Tufts University School of Medicine at the New England Center Hospital, Boston, Mass.; Edwin B. Astwood, M.D., F.A.C.P., Director.																18–22 X
Course No. 8, MODERN CONCEPTS OF INTERNAL MEDICINE: State University of Iowa College of Medicine, Iowa City, Iowa; William B. Bean, M.D., F.A.C.P., Director; J. Maclean Smith, M.D., F.R.C.P. and S. (Glas.), Associate Director; George N. Bedell, M.D., and William P. Jolly, M.D., Assistant Directors.																

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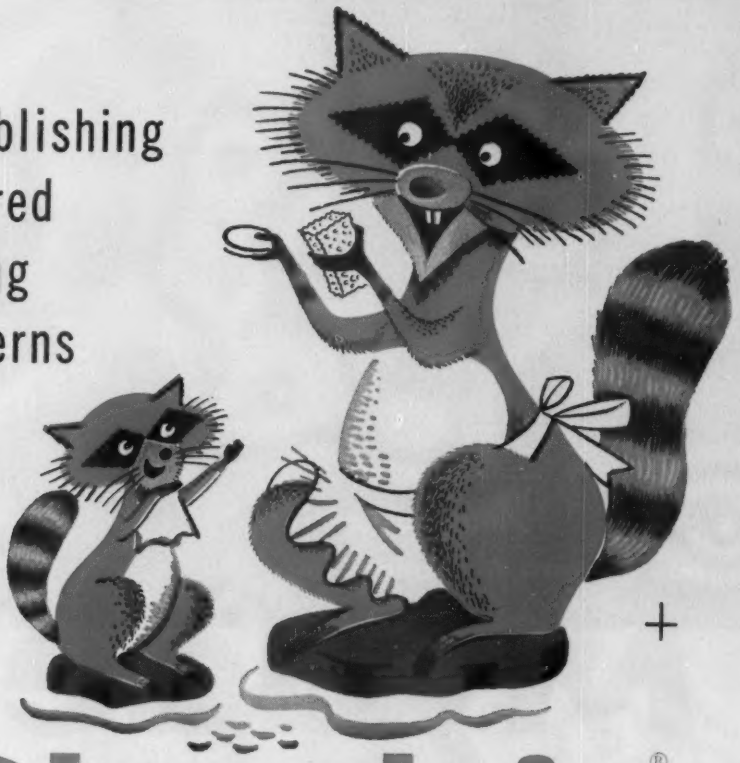
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*de Planter Bowes, A.: Nutrition of Children During Their School Years, *Am. J. Clin. Nutrition* 3:254, 1955.

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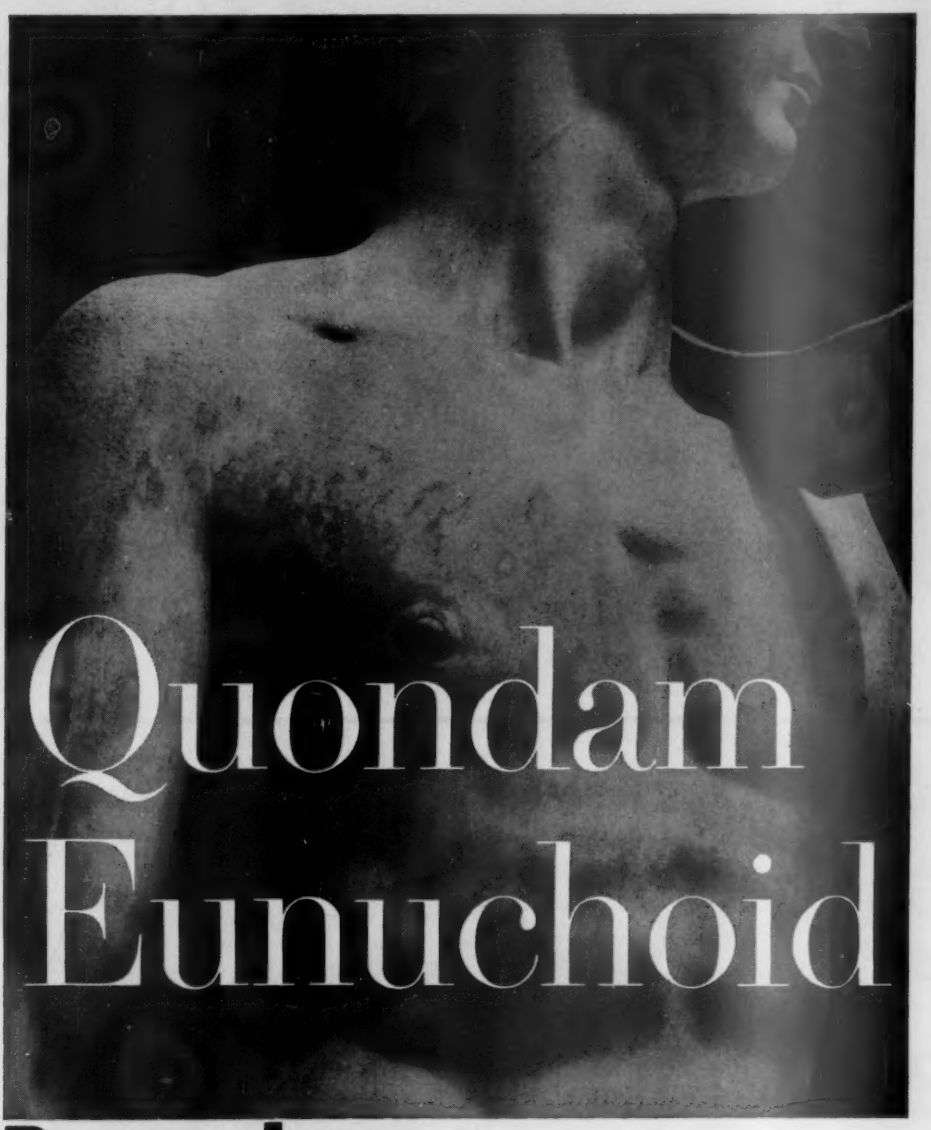
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2. Sebrell, W.H., Jr.: J.A.M.A., 152:42 (May, 1953).
3. Sherman, R.J.: Medical Times, 82:107 (Feb., 1954).

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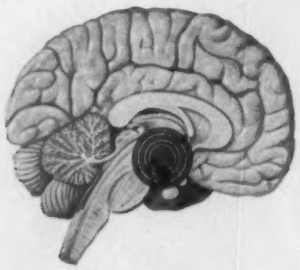
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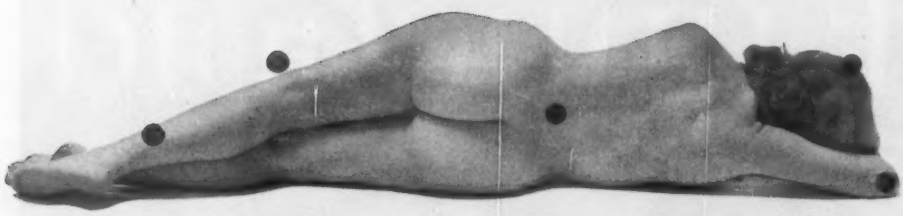
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1. Reiss, F. (New York City): Psoriasis and Stress, presented at International Medical Congress, Verona, Italy, Sept. 1, 1955.

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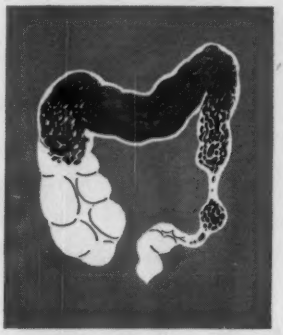
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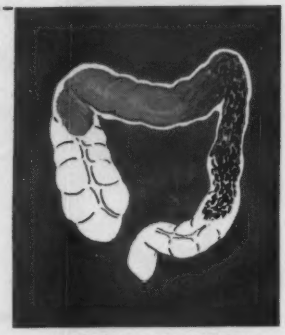
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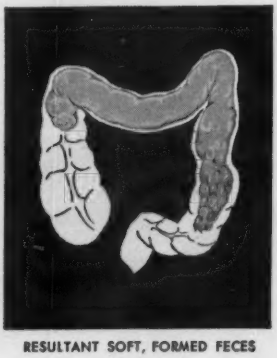


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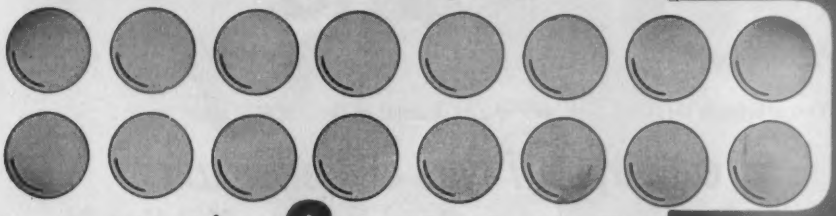
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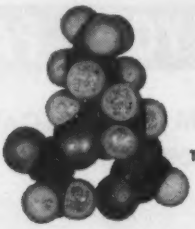
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1. Selling, L. S.: J.A.M.A. 157: 1594, 1955. 2. Borrus, J. C.: J.A.M.A. 157: 1596, 1955.

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*Reifenstein, E. C., Jr., in Harrison, T. R.: Principles of Internal Medicine, ed. 2, New York, The Blakiston Company, Inc., 1954, chap. 98, pp. 702, 703.

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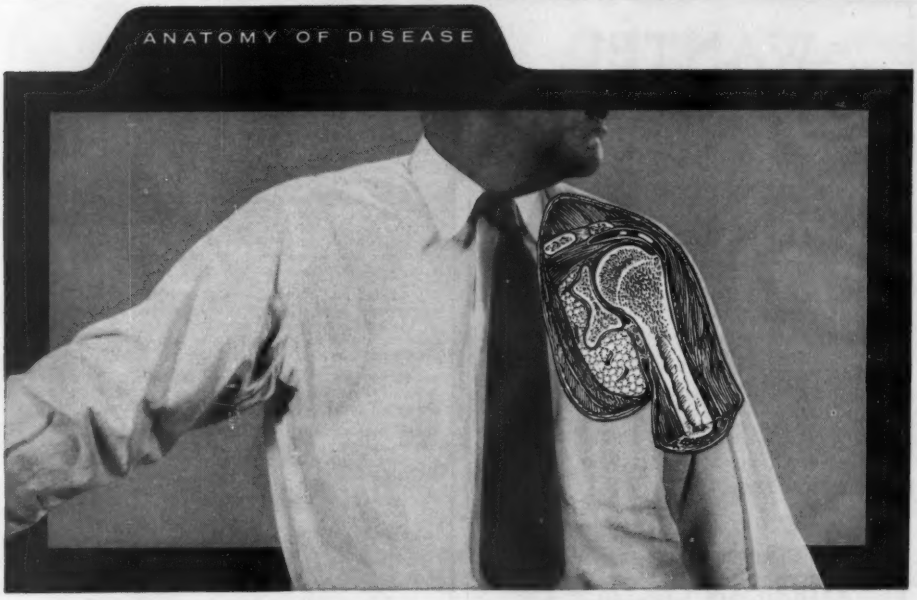
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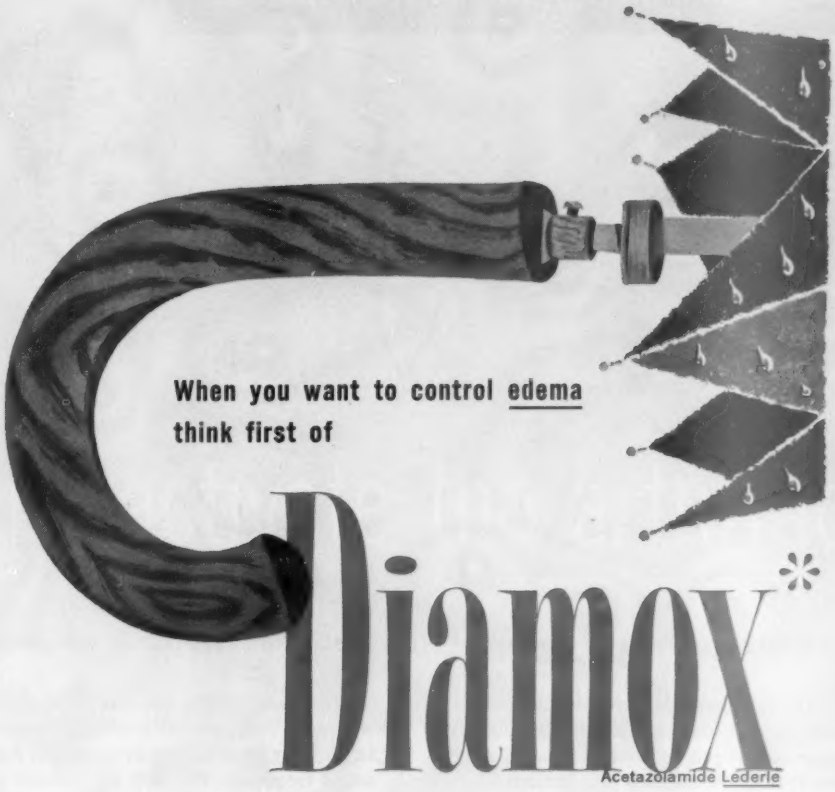
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1. Moyer, J. H.; Dennis, E., and Ford, R.: A.M.A. Arch. Int. Med. *96*:530 (Oct.) 1955.
2. Wilkins, R. W.: J. Chronic Dis. *1*:563 (May) 1955.
3. Moyer, J. H.: Texas J. Med. *51*:693 (Oct.) 1955.

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References: 1. Bunim, J. J., et al.: J.A.M.A. 157:311, 1955. 2. Forsham, P. H., et al.: Paper presented at First Internat. Conf. on Prednisone and Prednisolone, New York, May 31-June 1, 1955. 3. Perlman, P. L., and Tolksdorf, S.: Scientific Exhibit presented at A.M.A. Annual Meet., Atlantic City, June 6-11, 1955.

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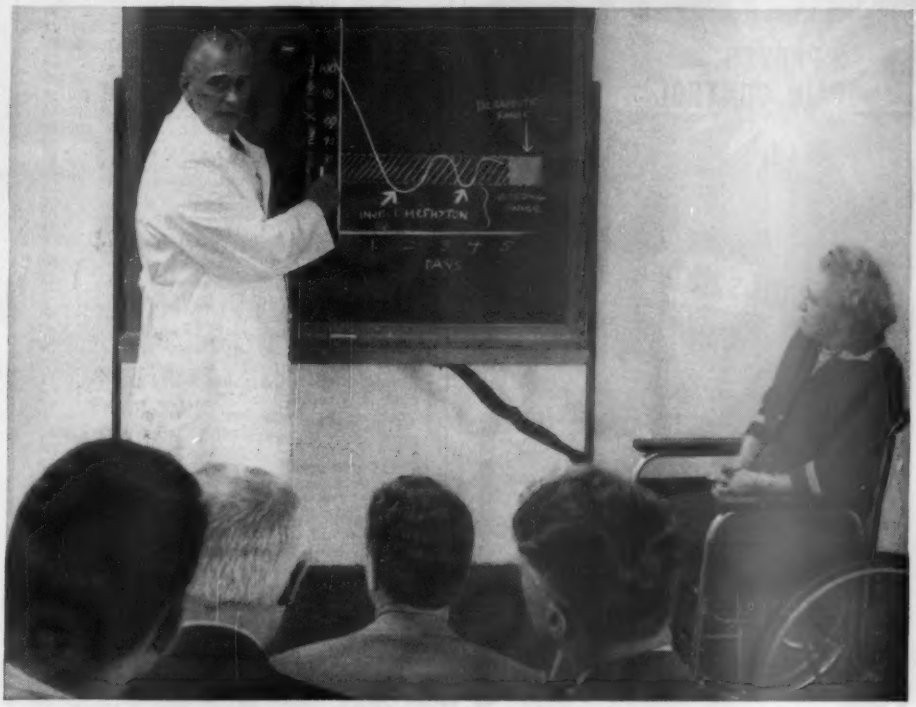
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1. Gamble, J. R., *et al.*, *Arch. Int. Med.* **95**:52, January 1955.

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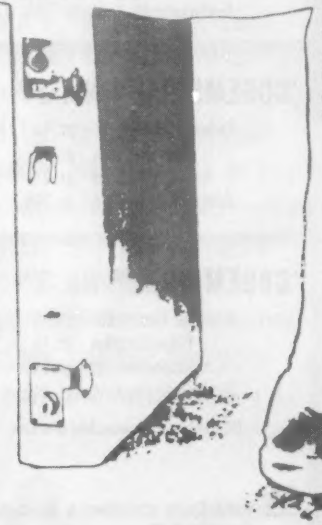
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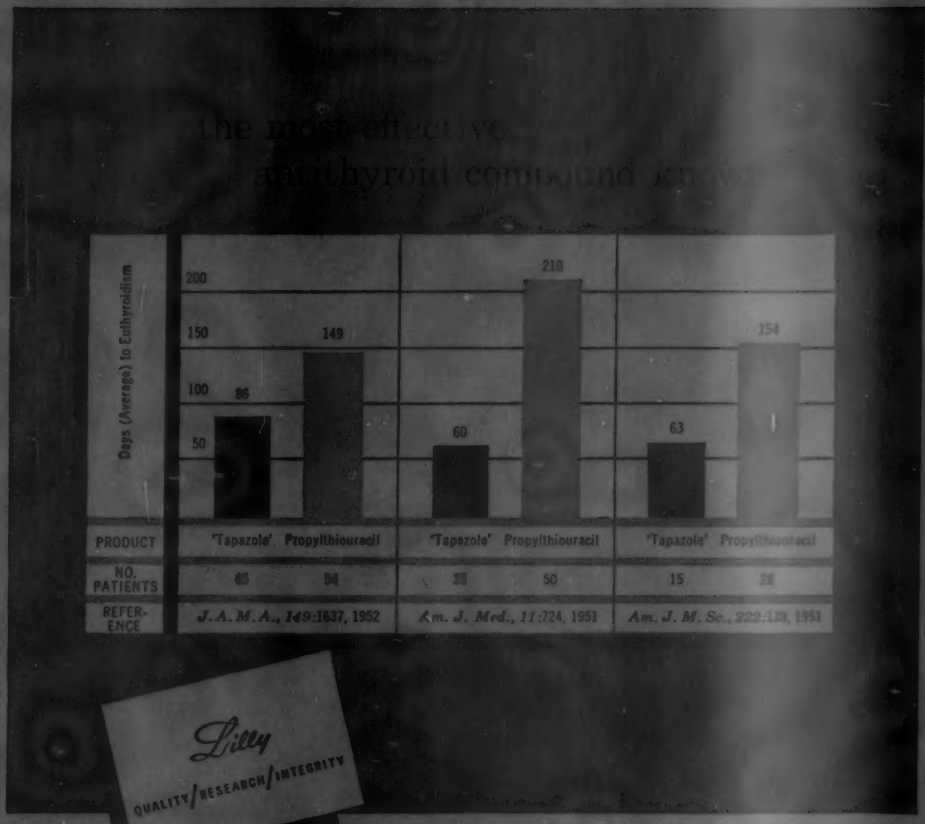


References: 1. Pocock, D. G.: Personal communication. 2. Harding, C. W.: Personal communication. 3. Hollander, W. M.: Personal communication.

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*J. Clin. Endocrinol., 14:948, 1954.

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